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Editor
ROY WALDO MINER

THE COLON ITS NORMAL AND ABNORMAL PHYSIOLOGY AND THERAPEUTICS*

Organizing Chairman M L TAINTER
Conference Chairman THOMAS P ALMY
Consulting Editor M L TAINTER

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Part III Pharmacology of the Abnormal Colon

Part IV Therapeutic Management of Colonic Disorders



INTRODUCTION TO THE COLON: ITS NORMAL AND ABNORMAL PHYSIOLOGY AND THERAPEUTICS

By Thomas P. Almy
Cornell University Medical College, New York, N. Y.

It has been a long time since any substantial group of investigators has assembled for the sole purpose of discussing the colon. As a matter of fact, in the memory of all those whom I have consulted on the matter this is a conference without precedent.

The reasons for the neglect of this subject are not hard to see. We are all aware of a gradual emergence over the last half century from a Victorian reticence about anything that has to do with the pelvic viscera. I think perhaps that even among physicians and scientists, this has stood as somewhat of an obstacle to the full scale objective study of problems of this nature. Secondly, as you know, technology in other lines has advanced rather more rapidly than in those we can apply to study the colon and, in simple fact, workers in other fields have had more about which to talk and confer. But even in the field of gastrointestinal research the colon has been a subject of less than average attention because of the complexity of many of its processes, such as its motor functions and its bacteriology.

But aside from the previous neglect of this subject, is it important enough for a group of this kind to devote two days to discussing it? The significance of colon disease is impressed upon us in many ways. Any practicing physician will tell you that among the most common and most troublesome problems he encounters in practice are those of habitual constipation and functional colonic disorders. This condition is reflected in the statistics of illness in industrial populations where the functional gastrointestinal disorders rank second only to the common cold as a cause of absence from work due to illness. Patients affected by functional colonic disorders seldom are very sick, but in the aggregate they constitute a large medical and socio-economic problem. Second, as you know, on our national list of causes of death is cancer, and 15 per cent of all cancer in man occurs in the colon. One tenth of all human cancers can be seen by looking through a single instrument, the proctoscope. We shall not include in our discussions either cancer of the colon or specific infections of the colon, yet I believe that from the basic physiologic processes which we shall cover, we may learn things of considerable importance to our understanding of those major health problems.

This conference has been conceived as an interdisciplinary conference in which investigators who have studied the colon in many different ways may communicate with each other. The theme then is *communication* and, to communicate freely between scientific disciplines, we must have real understanding of our terminology. I urge, therefore, that all of us use such simple and broadly understandable terms that we shall not make of our discussions another tower of scientific babel.

Part I Physiology and Pharmacology of the Colon

NORMAL PHYSIOLOGY OF THE COLON OF ANIMALS

By J Paul Quigley
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The two animals in which the physiology of the colon has been studied most thoroughly are the dog and the human I shall accordingly emphasize the physiology of the colon as it has been reported in these two animals

Metchnikoff Arbutnott Lane and others have maintained that the large intestine is not essential to the human In fact it was considered to be a redundency and the cause of so many systemic diseases and disorders that it interfered with human longevity As we have learned more about colon function in health and disease less emphasis is placed on autointoxication and other objectionable aspects of colonic function It is now recognized that although life is possible in animals and in man following complete colectomy the colon nevertheless normally fulfills several important functions Our more accurate appreciation of colon function in health and disease has resulted from a large number of recent studies of the colon of man and animals by a variety of experimental methods

Colon activities are (1) to receive and store material (2) to propel and discharge material (3) to absorb water salts *etc* (4) to secrete and excrete (5) to serve as an area for initiating afferent impulses and (6) to provide a location for the action of bacteria which release food substances and produce vitamins gases and toxic substances The small and large intestine are similar since propulsion secretion and absorption occur in each but these activities occur much more slowly in the colon

The phylogenetic development of the colon has been partly determined by the diet of the species and in turn the form and activity of the colon probably influences the optimal diet of the species The human colon reflects the omnivorous diet of this species and in form and function it lies between that of the carnivora with a short straight type of colon having a rudimentary cecum and the long sacculated colon with capacious cecum of the herbivorous species

The colon is relatively large and distensible Thus it is especially designed to provide large capacity This factor and its specialized musculature permit long retention of its contents The longitudinal muscular coat in man and some animals is arranged into taenia coli Since the taenia when exhibiting normal tone are somewhat shorter than the remainder of the colon they draw the colon into saccules These are supplemented by folds of the mucosa to produce sacs or pockets in the colon

The large intestine has considerable mobility This is especially noticeable in the human transverse and pelvic colon where the long mesentery permits a wide range of movement The human cecum ascending colon and hepatic flexure also possess considerable mobility but the splenic flexure descending colon and rectum are relatively fixed The floating character of the colon

permits great variation of position in response to posture, respiration, gas distention, and especially variation in smooth muscle tone (Barclay[1]).

Considerable ingenuity has been employed in studying the motility of the colon. Colon motor activity has been studied extensively by the X ray and balloon technique, some investigations have been made by the injection of thorotrast under the serosa, and intralumen pressure has been measured by the transducer technique. In contrast to the extensive studies with isolated strips of small intestine, relatively few investigators have studied isolated sections of the large bowel, but transplants and *in vitro* strips of colon have been studied. Some observations have been made of colon movements *in situ* when the abdomen of anesthetized animals or humans is opened, or in animals through abdominal windows.

Colonic movements are rather irregular and unpredictable, but like movements in other portions of the gut, they are augmented by distention from food residues, gases, fluids, *etc.* They consist of nonpropulsive segmentationlike contractions called "haustral churning." These movements are chiefly effective in mixing the colonic contents and in exchanging the portions in contact with the mucosa, thus they aid greatly in colonic absorption. Forsell and Hurst[2] ascribed the haustral movements to contractions of the muscularis mucosa, but these movements are not limited to the mucosal folds, and they appear to be much more powerful than the muscularis mucosa could produce. Probably they result primarily from activity of the longitudinal muscles which, on shortening, force the colon wall into accordionlike folds and thus produce the clefts and haustra. Contractions of the circular muscles probably also contribute to the haustral movements. In fact, the haustral contractions observed in the open abdomen of men and animals indicate their origin from simultaneous contractions of the taenia and bands of circular muscle (von Bergmann[3]). The colonic contents are forced into these sacculations. Fecal material in some animals becomes sufficiently inspissated in this form to produce scybala. Haustral churning mixes the contents thoroughly and brings it into contact with the mucosa so that absorption and uniformity of composition is promoted. At infrequent intervals a "mass contraction" occurs in a section of the colon so the contents are expelled. As the contraction subsides, the material may return to its former position. Occasionally, as in response to the gastro-colic reflex, mass peristalsis may involve the entire proximal colon so the contents are shifted from one section to the next and a desire for defecation may follow.

Bayliss and Starling[4] and Elliott and Barclay Smith[5] saw waves pass in the dog's exposed intestine from the ileum to the midcolon. They did not observe antiperistalsis *in the proximal colon of the dog, but in the cat, rat, guinea pig* and other mammals, they and several others have noted antiperistalsis in the proximal colon. Zondek[6] observed the dog's colon through a celluloid window in the abdominal wall. He saw peristaltic movements occurring regularly every thirty seconds. The frequency of movements was reduced during starvation and increased on the ingestion of food.

The studies made by numerous investigators with the balloon technique on unanesthetized dogs (Welch and Plant,[7] Quigley and Solomon[8]) were essentially

in accord that the dog's colon usually is relatively inactive and motility is irregular It develops weak contractions or is quiescent much of the time but more pronounced activity occurs at intervals of approximately 15 to 30 minutes This activity consists of more vigorous contractions superimposed on increased tone and lasting for 4 to 15 minutes The colon resembles other portions of the digestive tract for its irritability is influenced by the volume of its contents The tone and contractions are greater and more continuous if the colon is distended by normal contents or by a large balloon A wide range of colon activity may occur and it may vary from persistent high tone with almost continuous motility and brief periods of relaxation to prolonged inactivity and short infrequent contractions

Templeton and his associates made a detailed study of the dog s colonic motility by employing six balloons arranged in tandem (Templeton and Lawson[9] Adler and Templeton[10]) Their studies emphasize the variability of colonic motility but certain patterns of activity were noted The entire colon may show related activity For example weak rhythmic contractions may occur over the entire colon or especially in the distal half This activity may suddenly change in form and pressure waves may move either anal or oralwards Activity consisting of vigorous contractions superimposed on elevated tone may start in the ileocolic region and progress with gradually decreasing magnitude to the anal end of the colon Apparently weaker contractions correspond to the nonpropulsive haustral segmentation contractions which periodically occur in the human colon The more vigorous activity resembles the large colon movements' or the mass movement described by Holzknecht,[11] Barclay [12] Hertz [13] and others Templeton and his associates observed that these progressive contractions frequently were followed by less vigorous contractions occurring simultaneously in all parts of the proximal colon while the distal colon was inactive Reversed movements in the dog s proximal colon were observed by Templeton A reciprocal relation was frequently observed especially in regard to the progressive contractions of the proximal and distal colon When the motility and tone of one portion was augmented the other area was depressed Rhythmic (nonprogressive) contractions might occur in one section without affecting the other region The rhythmic contractions were rather definitely attributable to circular muscle activity The reciprocal relation between the proximal and distal sections which Templeton observed in the intact colon was also present after transection of the colon but peristaltic waves did not pass the cut portion of the colon Templeton also obtained evidence that activity of the longitudinal muscles of the distal colon was reciprocally related to the circular activity of that segment but tended to occur simultaneously with the progressive wave of contraction of the proximal colon This activity should be effective in propelling material from the proximal to the distal colon Contractions of the longitudinal muscle frequently were associated with evidence of the animal s distress and an attempted defecation

The mass movement observed by Holzknecht Barclay and Hertz occurring in the colon shortly after feeding an additional radio-opaque meal probably constitutes the normal propulsive movement in the colon and occurs three to

four times a day, the colon remaining relatively inactive the remainder of the time Hertz recognized that ingestion of food is the chief stimulus for this activity which he designated as the gastrocolic reflex The effect on the dog's colonic motility of the activities associated with eating was carefully studied by Welch and Plant[7] They noted that when the colon contained its normal contents and the recording balloon was of moderate size, ingestion of food by the dog or even entrance into the room of the man who usually fed the dog promptly *augmented colonic motility and tone for about 15 minutes Sometimes this* reaction could be repeated three or four times If the colon was empty at the time of feeding the reflex usually was not elicited Placing the food into the stomach through a fistula failed to augment colon activity Thus the reflex is not due to gastric filling as Hertz believed, but is a feeding reflex It is dependent on appetite and the heightened irritability of the colon associated with the existence of a full bowel According to Reagan and Puestow[14] feeding had no effect on isolated segments of the colon The gastrocolic reflex was absent after the colonic wall was sectioned

We have observed that, in well trained dogs colonic motility retained the *same fundamental pattern over periods of several months Colonic motility was* not significantly changed by moderate sounds the movement of individuals in the room, or when the animal fell asleep Noxious stimuli such as the application of electric or other stimuli to the skin frequently inhibited colonic motility although at times a general increase in motility or no effect was elicited Templeton and Borkon[15] obtained similar results from more extensive studies A brief period of exercise in the dog produced a marked increase in colonic motility, but according to Steinhaus and de Young[16] the motility was subnormal following the exercise

Moderate distention of the colon by its normal contents or a medium sized balloon according to Welch and Plant[7] usually augmented colonic tone and motility *Motility was slight or absent however when the colon was excessively distended* by a large balloon Lawson and Templeton[9] moderately distended the proximal colon of the dog with a balloon or mineral oil and produced temporary augmentation of proximal colonic tone and motility The introduction of 200 cc of water saline or soapsuds into the dog's colon first produced colonic inhibition but this was usually followed by increased motility Mechanical irritation or electric stimulation of the anal sphincter area increased the tone and motility locally, but depressed the activity and tone of the proximal colon Numerous investigators have noted that colonic stimulation by distention or the introduction of such irritants as turpentine delayed gastric evacuation Indirect methods of study have indicated that the retarded emptying resulted from pylorospasm *Quigley and associates*[17] *employed* more direct methods of study and concluded that in the dog the delay of gastric emptying produced by reflexes from the colon resulted from reduced evacuation motility in the gastric antrum and occurred in spite of a relaxed (open) pyloric sphincter Ivy and associates[18] noted that in the dog constipation, irritation of the colon or stimulation of the nerves from the colon inhibited the flow of bile Mechanical irritation of the rectum or lower colon of the dog inhibits the jejunum (Steinhaus[19]) Normally impulses from the

colon do not reach conscious levels except when the rectum is distended and produces a desire to defecate Many workers have presented evidence that sensations associated with constipation can be produced by distending the colon with a balloon or with cotton This claim was not confirmed by Hines Lueth and Ivy[20]

Stress reactions such as exposure to cold pain, hypoglycemia or worry were observed by Almy and associates[21] to augment the colonic tone Ingersoll and Jones[22] noted that faradic stimulation of structures within the thalamus hypothalamus or telencephalon of the cat produced a variety of effects on the colon probably owing to a variable degree of stimulation of the parasympathetics and sympathetics The effects were diminished by blocking the sacral parasympathetic outflow to the colon Ranson *et al* [23] obtained increased colonic motility by stimulating the anterior hypothalamus Masserman and Haertig[24] obtained similar results with weak stimulation of the anterior hypothalamus but inhibition followed strong stimulation of any portion of the hypothalamus Sheehan[25] increased colonic motility by stimulation of the preoptic region but inhibition of the colon was usually produced by stimulating any portion of the hypothalamus especially the lateral hypothalamus

Garry[26] reviewed the extensive literature regarding the innervation of the colon. The colon is similar to other portions of the gut since it possesses considerable autonomy especially in the proximal portion and the haustral contractions may be intrinsic phenomena Local reflexes may be produced through the myenteric plexuses but these reflexes colonic tone and the mass movements are greatly influenced by the autonomic nervous system through the thoracicolumbar and sacral fibers Although the influence from the sympathetics usually reduces colonic tone and motility other effects have been reported Strong emotions which are usually associated with a generalized sympathetic discharge may result in diarrhea and other manifestations of colonic stimulation

The effects of the extrinsic nerves on colonic motility vary somewhat depending on the degree of tone and motility at the time of stimulation Usually the sympathetics inhibit the colon but when colonic tone is low sympathetic stimulation can augment motor activity Sympathectomy of the colon usually has not removed inhibitory control No abnormality in colonic function was observed by Cannon[27] by exclusion of the thoracicolumbar fibers When interpreting such experiments it should be recognized that many of the conclusions drawn from acute experiments or under normal conditions may not be supported by those following prolonged modifications because of the development of compensatory factors or adaptive changes

Learmouth and Markowitz[8] reported that inhibitory fibers to the distal colon of the dog pass with the mesenteric artery Motor fibers from the pelvic nerves ascend the wall of the colon Wells Mercer Gray and Ivy[29] observed that parasympathetic influences in the dog pig and monkey reach the colon by the pelvic nerve and produce contraction of the longitudinal and circular muscles The fibers to the distal colon pass directly but those to the proximal colon pass along the colon wall Contraction of the colon did not follow vagus stimulation in the dog but occasionally the cecum of pigs and monkeys did

respond Electric stimulation of the hypogastric nerves sometimes produced contraction of the circular muscle but only in the distal colon Rentz[30] reported that the motility of the proximal colon of guinea pigs and rabbits is sometimes increased by vagal stimulation In general, the studies on animals or human subjects has shown that the vagi have little or nor direct influence on the colon Holman Wolf and Wolff[31] observed that the effects on the proximal colon of drugs emotional states the gastro colonic reflex, lysozyme secretion *etc* were not altered in a human subject by vagotomy Thus there is no good reason to anticipate significant, direct effects on the colon by sectioning the vagal fibers Actually it was observed that emotional states and other factors were as effective in producing colonic hyperemia hypermotility increased lysozyme secretion *etc* after vagotomy as before these nerve fibers were sectioned Lannon and Weller[32] also concluded that the parasympathetic nerves travel to the human distal colon from the sacral cord independent of the blood vessels and end in association with intermural colonic nerve plexuses Stripping the mesenteric artery or perisacral neurectomy should not disturb parasympathetic function in any part of the colon However resection of the rectum or pelvic colon would destroy the parasympathetic supply to the colon

Scott and Cantrell[33] were unable to demonstrate in the dog or human any change in colonic tone or motility following section of the vagi or hypogastric nerves Division of the pelvic nerves produced hypotonicity and hypomotility of the colon but megacolon fecal impaction or diarrhea did not develop

The investigations of Florey[34] indicate that augmented colonic parasympathetic stimulation in the cat results in increased colonic vascularity motility and secretion of mucus These results followed stimulation of the nervi erigentes or from cholinergic drugs or stimulation of the central end of one nerve the other nerve being intact Simultaneous stimulation of the pelvic nerve and the sympathetic nerves emanating from the inferior mesenteric ganglion inhibited colonic motility produced vasoconstriction and decreased mucus secretion Stimulation of the sympathetic fibers alone did not alter mucus secretion

The protective diluting and lubricating action of mucus (the mucus barrier) against the action of irritants or bacteria on the underlying mucosa cells throughout the digestive tract is well recognized and has been especially emphasized by the recent work of Hollander Wolf and Wolff and of Almy Mucus probably protects the mucosa against mechanical injury by reducing friction and dilutes or neutralizes irritating chemical substances in the colon as in other portions of the gut Since according to Florey[34] the colonic secretion is alkaline it protects the mucosa against injury from the acid products of bacterial activity Mucus secretion by the colon is augmented following colon irritation (severe purgation prolonged irrigation—clinical conditions such as mucus colitis ulcerative colitis following severe psychic trauma) Probably this increased secretion is an attempt to provide a protective mechanism The mucosa examined through a sigmoidoscope in the human or through exposure of the mucosa in animals have been seen to develop increased vascularity (hyperemia) and mucus production after normal defecation and especially after

the introduction of soap glycerine turpentine and other irritants into the lower colon (Larson and Bargen[35]) These procedures may also increase the size of the mucosal folds and produce a marked increase in colonic tone and motility Similar results follow the systemic administration of cholinergic drugs (White and Jones[36]) Mechanical injury or injection of cholinergic drugs produced severe spasm in colon explants (Lium and Porter[37]) This effect was associated with increased secretion from the goblet cells and hyperemia

The material discharged from the ileum to the colon closely resembles diluted feces It contains the remains of the digestive juices much cellular debris connective tissue and cellulose (if the latter two substances have been ingested) and numerous bacteria No enzyme is produced by the digestive tract which acts on connective tissue and cellulose even in such forms of life as the termite whose diet consists largely of cellulose but the bacteria digest the cellulose and liberate food substances This digestion occurs in the ileum cecum and proximal colon where bacteria find favorable conditions for multiplication and activity A significant portion of the food may be released by such bacterial activity in herbivora in which the cecum is extensive to provide prolonged exposure of plant structures to the bacteria Indole skatol various gases and vitamin K B_{12} biotin niacin thiamine riboflavin *etc* are produced by this bacterial action[38, 39] Probably most animals and human beings in particular are rarely provided with a completely balanced diet They apparently rely upon the synthetic activities of their intestinal micro organisms to provide many of the deficient factors Normally the digestive tract functions very efficiently and almost all the available fat carbohydrate and protein ingested as food has been absorbed from the material discharged through the ileocecal valve

A significant amount of water and salts is absorbed from the proximal (absorbing) colon but relatively little absorption takes place in the distal (storage) colon Thus the feces contain about one fifth as much water as the ileal discharge In the human this involves the absorption of approximately 500 cc of water per day from the 620 cc passed through the ileocolic sphincter leaving 120 cc in the form of feces Following the production of an ileostomy watery material is at first passed through the ileal fistula and there is a tendency to dehydration Later the ileum adapts by absorbing more water and the discharge closely resembles normal feces

Normal feces have a water content of 65 to 80 per cent The solid matter is approximately one third bacteria most of which have died in the unfavorable environment encountered in the distal colon Much of the remainder is derived from the digestive juices (chiefly bile pigment mucin and cellular debris) and 2 or 3 per cent nitrogen 10 to 20 per cent fat and 10 to 20 per cent inorganic matter The fecal fat is in the form of split and unsplit fat The neutral fat is derived from bacteria and broken down epithelial cells The split fat is unabsorbed fatty acids from the diet It is diminished on a low fat diet The percentage of nitrogen in the feces is altered only slightly by the amount of protein ingested

The normal fecal excretion for dogs was found[40] to be 2 11 to 3 99 per cent

fat (mostly fatty acid) the carbohydrate content of 1 0 to 3 0 per cent was not much affected by variations in the diet The percentage of dietary fat or protein lost in feces varied inversely with the amount in the diet

The most abundant salts in the stool are calcium and phosphate Recent evidence indicates that the colon does not specifically excrete metals, for no substantial amounts of calcium, iron, or other metals were found in the isolated colon [40] L'Heureux Tweedy, and Zorn[41] administered radioactive calcium to rats and concluded that it was not actively excreted by the colon Maddock and Heath[42] concluded from histological studies of the digestive tract and a colonic explant that no iron is excreted by these organs Cance and Widdowson[43] also obtained evidence that iron calcium and magnesium are not eliminated by the intestinal mucosa

The normal feces are brown colored owing to the presence of the modified bile pigments stercobilin and urobilin The color may vary somewhat, however with the diet Diets high in meat tend to be much darker, while the ingestion of much milk imparts a very light color to the feces The presence of much fat in the stool produces a pale color, and this is especially marked if bile pigments are absent as in common bile duct obstruction Blood in the stool causes a red dark brown or black coloration depending on whether the blood enters the gut in the lower or upper regions The odor of feces is attributable mainly to indole skatol mercaptan hydrogen sulfide *etc* The average pH is 7 to 7 5 on the outside of the mass but the interior where bacteria may have produced much organic acid may have a pH as low as 5

Even during prolonged fasting a small quantity of fecal matter is formed and excreted It is produced from endogenous sources and has much the same components as feces produced during normal alimentation

Adam[44] reported that the rate of glucose absorption from the colon of anesthetized dogs is proportional to the glucose concentration but the rate is always moderate The optimal concentration is 5–5 4 per cent and this was independent of the blood glucose level These observations are essentially in accord with the numerous studies on glucose absorption from the colon of human subjects (McNealy and Williams[45]) Protein split products are absorbed in significant amounts from the colon but at a slower rate than from the small bowel Rhoads *et al* [46] reported more rapid absorption of the products from tryptic digestion of Witte s peptone than from acid hydrolysis of casein Ravdin[47] has also reported the absorption of significant amounts of amino acids administered rectally

Conclusion —The anatomy and physiology of the colon are very closely allied In structure the colon is a loose sack with thin muscle walls Thus its contents can stagnate or periodically be mixed propelled or expelled The limited blood and lymph supply indicates that secretion and absorption are moderate in magnitude The colon is located at the lower end of the digestive tract to perform those functions neglected by the more proximal portions of the gut But since the proximal gut is very efficient in digesting and absorbing food and fluids the colon can perform its limited duties in a relatively lazy fashion It is not expected to do a great deal of work but usually it does very well what

is required The colon resembles the caboose on a freight train its functions may be less essential than those of the engine or the freight cars but it does serve a purpose

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Discussion of the Paper

DOCTOR FRANZ J INGELFINGER (*Boston University Medical School Boston Mass*) Would Doctor Quigley distinguish from a clinical standpoint between propulsive and nonpropulsive motility as the result of the colon stimulation of the hypothalamus? Does the colon need any pharmacologic agent? Does it stimulate propulsive or nonpropulsive motility?

DOCTOR QUIGLEY In my own work I have tried to so distinguish Weak contractions, which I indicated might be recorded by the balloon water technique are not propulsive, they are haustral churning movements The large contractions superimposed upon tone change however are, in most cases, propulsive in character according to the observations of most individuals

AUTONOMIC AND PHARMACOLOGIC CONTROL OF COLONIC ACTIVITY

By George B Koelle
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The correlation of data obtained from animal experimentation and from clinical investigations on colonic activity is extremely difficult because of the marked differences in anatomy innervation and functional patterns which exist. The similarities that are present among different species appear to be more closely coincident with their dietary habits (carnivorous herbivorous or omnivorous) than with their phylogenetic classifications as was shown in an early paper by Elliott and Barclay Smith [1] Sir Henage Ogilvie[2] has presented a highly entertaining and informative analysis of the relationship between the life habits in general and colonic structure and function in various mammals The extremes in differentiation can be exemplified by comparing the colons of the herbivorous rabbit or koala bear where the cecum is a highly developed and functionally important portion with those of the carnivorous dog or omnivorous man in which this appendage is of insignificant size and of little importance with respect to absorption The physiologist meets with another difficulty in attempting to assess the roles of the intrinsic neural networks and the various humoral agents in the regulation of colonic motility The great majority of investigations in this field have been conducted on the small bowel but to what extent it is justifiable to apply to the colon the conclusions reached from such studies is disputable With these limitations in mind and autonomic and humoral factors which may regulate colonic activity will be considered

Innervation

The sympathetic and parasympathetic innervation of the colon in mammals has been reviewed by Garry [3] In man the preganglionic fibers of the sympathetic or lumbar outflow arise from the first and second lumbar segments of the spinal cord pass through the sympathetic trunks and give rise to the pelvic splanchnic nerves These enter into the intermesenteric plexus then continue as the intermesenteric nerves to the inferior mesenteric plexus where most of the extracentral synapses probably occur in the two to four inferior mesenteric ganglia The postganglionic and possibly a significant number of preganglionic fibers then proceed as the inferior mesenteric nerves to the colonic wall

The sacral division of the parasympathetic supply originates from the third and fourth sacral segments of the cord and reaches the colon via the hypogastric plexus Recent evidence[4] confirms earlier suggestions that the vagus supplies parasympathetic preganglionic fibers approximately to the proximal half of the human colon In addition to the medullary parasympathetic center there is possibly an independent center in the lumbosacral region of the cord since functional activity of the colon is relatively unimpaired following high transverse lesions [5] The pudendal nerves which contain the motor fibers to the

Discussion of the Paper

DOCTOR FRANZ J. INGELFINGER (*Boston University Medical School, Boston, Mass.*): Would Doctor Quigley distinguish from a clinical standpoint between propulsive and nonpropulsive motility as the result of the colon stimulation of the hypothalamus? Does the colon need any pharmacologic agent? Does it stimulate propulsive or nonpropulsive motility?

DOCTOR QUIGLEY: In my own work I have tried to so distinguish. Weak contractions, which I indicated might be recorded by the balloon water technique, are not propulsive; they are haustral churning movements. The large contractions superimposed upon tone changes, however, are, in most cases, propulsive in character, according to the observations of most individuals.

the response of the sigmoid tends to resemble that of the sphincters [16] The reverse of these effects is generally seen following sympathetic stimulation or the injection of epinephrine or norepinephrine Sympathetic or parasympathetic denervation produces at least temporarily the opposite effects from those of stimulation of the same outflows The foregoing statements require considerable qualification however since numerous exceptions have been reported The state of activity of the bowel at the time when nerves are stimulated or cut seems to determine to a great extent the type of response that ensues both qualitatively and quantitatively Many of the seemingly anomalous results that have been described might be explained by the assumption that both the sympathetic and parasympathetic preganglionic fibers synapse with varying proportions of adrenergic and cholinergic neurons This would by no means resolve all the discrepancies observed however since the responses to ACh and epinephrine–norepinephrine may also vary

The production of either excitatory or inhibitory responses in smooth muscle by both ACh and epinephrine has been discussed by Brown [17] The evidence he cites suggests two possible explanations for the dual actions of the mediators based on their concentrations a reversal of their effects at a given site or a change in their predominant site of action (*i e* on transmission or on the contractile mechanism) as their concentrations are increased Either explanation is consistent with the known influence of the pre existing state of activity on the type of response since that activity is probably determined to a great extent by the concentrations of the mediators which are already present Considerable work remains to be done to place these hypothetical considerations on a firm basis

Despite the importance of the autonomic nervous system as a whole in the regulation of the over all integrated activity of the colon a considerable degree of normal function is retained or regained following partial or complete extrinsic denervation Attention is thus focused on the control exercised independently by the intrinsic plexuses Here it is necessary to turn to studies on the isolated ileum where this factor has been analyzed more fully

Feldberg and Lin[18] have reinvestigated the peristaltic reflex in the isolated ileum of the guinea pig and rabbit When the intraluminal pressure is increased a contraction of the longitudinal muscle follows accompanied by an aboral wave of contraction of the circular muscle After the addition of sufficient d tubocurarine to paralyze the ganglion cells or cocaine to paralyze the nerve fibers the response of the longitudinal muscle was unaffected but that of the circular muscle was abolished A different approach was employed by Klinge [19] who studied the spontaneous and drug modified activity of cat ileum which had been stripped of various layers by a modification of the classical method of Magnus [20] Preparations consisting only of circular muscle exhibited no significant spontaneous contractions but the addition of ACh resulted in both localized and propagated contractions Physostigmine alone produced no such effects but enhanced the action of ACh In preparations containing circular muscle and the submucosal plexus there were spontaneous localized contractions but these were rarely propagated unless ACh was added All segments consisting of circular and longitudinal muscle and the myenteric

striated muscle of the external anal sphincter, arise from the second to fourth sacral divisions of the cord. With certain variations the general pattern of autonomic innervation of the colon in the dog and cat is similar to that in man.[3]

The intrinsic plexuses of the colon, the myenteric or Auerbach's and the submucosal or Meissner's plexus resemble those in the other regions of the gastrointestinal tract. It has generally been assumed that their ganglion cells give rise to cholinergic postganglionic fibers. Ambache[6] has recently studied *in vitro* the actions of nicotine on isolated segments of rabbit ileum which had been treated previously by local injections of botulinum toxin. This substance prevents the liberation of acetylcholine (ACh) by cholinergic fibers without interfering with the function of adrenergic nerves.[7] Instead of its normal stimulating effect, nicotine had an inhibitory action on the toxin treated segments, presumably due to the unmasking of the effect of adrenergic ganglion cells in the plexuses. Atropinization of isolated ileal and gastric strips from kittens likewise reversed the stimulant effect of nicotine.[8] The implication that the intrinsic plexuses in these regions contain both cholinergic and adrenergic neurons may apply to the colon as well.

A structural element which has been frequently overlooked in considering the intrinsic nervous pathways of the intestinal tract is the rich network of interstitial cells first described by Cajal.[9, 10] These cells which closely resemble Schwann's sheath cells in routinely stained preparations are most heavily concentrated in the immediate vicinity of the ganglion cells of the intrinsic plexuses between the longitudinal and circular muscle fiber layers of the muscularis externa and in the innermost region of the circular muscle layer. Their ramifying processes contact the processes of the neurons and each other and extend between the adjacent muscle fibers. Controversy has long existed as to whether they represent a primitive neural network or are merely supporting glial structures. Recently by the use of selective staining techniques Taxi[11] and Jabonero[12] have demonstrated convincingly that the interstitial cells are distinctive from glia and have thus reopened the question of their possible neuronal role. Suggestions as to their function include (1) the spread of impulses from postganglionic autonomic fibers of the ganglion cells of the plexuses to the muscle fibers by the liberation of humoral mediators, (2) the independent initiation of contractions, and (3) the integration of myogenic contractions through a primitive reflex mechanism. The determination of the functional relationship between the ganglion cells, the interstitial cells and the muscle fibers and the identification of the humoral agents involved constitute an interesting field for further study.

Motor Patterns

The characteristic types of contraction waves which occur in the normal and diseased human colon have been studied extensively and are described in detail in another paper in the present series.[13] Garry[3] and Youmans[14] have reviewed the known facts concerning their neural regulation. In general stimulation of the parasympathetic nerves or the administration of ACh or related drugs results in an increase in "propulsive" activity of the colon and a decrease in "mixing" activity and in the tone of the ileocecal and internal anal sphincters.[15]

(pseudo or butyro) ChE is localized in the membranes of the muscle fibers glial cells and many of the mucosal cells the highest concentrations being present in the interstitial cells Its function at various sites is much less certain On the basis of studies of triorthocresyl phosphate poisoning Earl and Thompson[25] suggested that in the central nervous system where it is localized in the glia and capillary walls it is probably concerned with the maintenance of the myelin sheaths The enzyme is similarly situated in autonomic ganglia There too it does not appear to be concerned directly with synaptic transmission [6] On the other hand the selective inhibition of the nonspecific ChE of the isolated ileum of the cat by diisopropyl fluorophosphate (DFP) resulted in a marked increase in the tone and spontaneous contractions of the longitudinal muscle[27] The conclusion that in the intestine the enzyme does function in the hydrolysis of a transmitting agent or local hormone received support from a study by Burn and associates [8] of the effects of X irradiation on rats One of the most prominent signs following exposure was diarrhea When the small intestines and colons of the irradiated animals were studied in the organ bath they were found to be selectively sensitive to ACh Comparison of their ChE activities with those of controls revealed that the nonspecific ChE was markedly reduced whereas the specific ChE was within normal limits The clinical counterpart of these results may be found in the earlier trial of DFP in the treatment of paralytic ileus by Grob and associates[29] Doses which caused little reduction of the specific ChE of the erythrocytes but greatly reduced the nonspecific ChE of the plasma resulted in a marked increase in peristaltic contractions of the colon It is reasonable to assume that there was a similar ratio for the degrees of inhibition of the two enzymes in the colonic wall

It might be asked whether the substrate normally hydrolyzed by the nonspecific ChE of the intestine of various species is ACh or some other ester In the rabbit the intestine contains no nonspecific ChE of the type found in the cat rat and man A benzoylcholinesterase[30] however which hydrolyzes benzoylcholine butyrylcholine and certain other esters but is relatively inactive against ACh is present in the same distribution pattern as the nonspecific ChE of the other species[31] Since ACh could hardly be the physiological substrate for this enzyme it is possible that other choline or related esters may have roles similar to those attributed to ACh at certain sites in the rabbit and perhaps other species Propionylcholine recently found in ox spleen by Banister Whittaker and Wijesundera[32] may represent one of a series of ACh like transmitting agents or local hormones the rest of which are yet to be identified

Epinephrine norepinephrine The predominantly inhibitory action of epinephrine and norepinephrine on the gastrointestinal tract with the exception of the sphincters and the possible presence of adrenergic neurons in the intrinsic plexuses have been mentioned The mammalian enzymes that have been shown to be capable of inactivating these mediators at significant rates include monoamine oxidase[33] cytochrome oxidase[34] conjugases[35] and DOPA oxidase[36] Both the former two are present in high concentrations in the intestine[37] but conclusive evidence is lacking as to which predominates in this function Inasmuch as the α methyl substituted sympathomimetic amines such as amphet

plexus exhibited spontaneous localized and propagated contractions The author's conclusions which are consistent with the observation of Feldberg and Lin were that the plexuses are essential for the initiation of spontaneous peristaltic contractions but not for their propagation Three possible mechanisms were proposed to explain the latter process the existence of protoplasmic bridges between the muscle fibers coordination by axon reflexes or propagation by mechanical stimulation Not suggested but certainly an additional possibility to be considered is the integration of the peristaltic waves by the network of interstitial cells In a recent more extensive investigation using similar techniques Evans and Schild[1] confirmed most of Klinge's findings but presented certain discrepancies emphasizing the fact that results obtained under such artificial conditions must be accepted with reservation

Humoral Agents

Certain aspects of the liberation actions and metabolism of ACh epinephrine norepinephrine, and other possible humoral agents of the intestine are considered below It should be reiterated that most of the information has been obtained from studies on the small intestine of laboratory animals, hence its applicability to the human colon is chiefly by inference

ACh The assumption that the ganglion cells of the intrinsic plexuses constitute the main source of the ACh liberated by the intestine has been questioned by Feldberg and Lin They found that during the perfusion of isolated rabbit ileum with saline solution the addition of 1 800 cocaine caused no reduction in its spontaneous output Since this concentration of cocaine is greatly in excess of the amount necessary to paralyze autonomic ganglion cells in the intestine and elsewhere but does not interfere with the response of the intestinal musculature to drugs which stimulate it directly they suggested the latter tissue as the chief site for the release of ACh Their view was strengthened by the finding that there was little quantitative correlation between the concentration of choline acetylase and the number of ganglion cells in various layers of the intestinal tract[3] It is difficult to reconcile this conclusion with the aforementioned findings of Klinge[19] in which segments containing muscle fibers but no ganglion cells exhibited no spontaneous activity until ACh was added Furthermore the output of ACh by the ganglion cells of the intestine *in situ* during preganglionic stimulation is probably considerably greater than what they might liberate under the conditions of the experiment cited Nevertheless it seems inescapable that a significant portion of the ACh synthesized by the intestine is from sources other than the ganglion cells The interstitial cells may also share in this process

Consideration of the distribution of the cholinesterases (ChE s) in the intestinal tract raises several questions It has been shown histochemically[4] that in the cat specific (true acetyl or aceto) ChE is present in the membranes of most of the ganglion cells and nerve fibers of the myenteric and submucosal plexuses A similar localization of the enzyme in known cholinergic neurons of the spinal cord and autonomic ganglia indicates that such ganglion cells of the plexuses are likewise cholinergic and that the primary function of the enzyme is presumably the hydrolysis of ACh The intestinal nonspecific

Congenital Megacolon

In collaboration with Doctors K Kamijo and R B Hiatt at the Presbyterian Medical Center New York an attempt was made to apply some of the findings of the experimental investigations discussed above to the study of a clinical condition congenital megacolon [45] This disease is characterized by spasm of the lower sigmoid and extreme dilatation or hypertrophy of the more proximal colon Over half a century ago Tittel[46] noted the complete absence of ganglion cells from the myenteric plexus of the lower spastic portion an observation which has been confirmed several times It has also been found that there are numerous thick closely packed bundles of nonmyelinated nerve fibers in the ganglion cell free myenteric plexus of the same region No similar structures are present in the dilated portion or in the corresponding region of normal specimens [47] The pathological findings and colonic motility studies in patients have led to the concept that the lack of propulsive peristaltic activity in the lower segment is due to the agenesis of the ganglion cells and that the dilatation of the proximal segment is a secondary compensatory phenomenon [48] Resection of the spastic segment is frequently followed by restoration of the normal appearance and function of the dilated portion [49]

In determinations of the relative ChE activities of surgical specimens of the proximal and distal regions we found that both specific and nonspecific ChE were considerably more concentrated in the latter Control specimens showed no corresponding regional differences Histochemical examination revealed that the relatively low values for nonspecific ChE in the dilated portions were attributable to a thinning-out of the structures with which the enzyme is associated The difference in specific ChE activity however appeared to be attributable chiefly to its presence in the excessive nerve fiber bundles of the spastic distal segment The presence of specific ChE and the absence of myelin sheaths indicate that the bundles are composed of cholinergic postganglionic fibers Thus the cholinergic neurons of the myenteric plexus may not be absent but displaced centrally and their fibers may reach approximately normal sites of termination To account for the spasm and lack of propulsive activity it might be postulated that the basic defect is an absence of adrenergic neurons The evidence for the presence of the latter in the normal myenteric plexus has been discussed earlier [8, 9]

Considerably more work is obviously required before this proposed hypothesis of the etiology of congenital megacolon can be considered as more than tentative It does serve to demonstrate that the gap between the theoretical and clinical aspects of colonic function is not too wide to be bridged by available investigative methods

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amine and ephedrine are inhibitors of monoamine oxidase, part of their pharmacological actions has been attributed to this effect, with the consequent accumulation of endogenous epinephrine and norepinephrine[38] The matter has been the subject of considerable debate but remains unsettled[39, 40]

During the past several years, evidence has accumulated for the presence of additional transmitting agents in the gastrointestinal tract The prevention of nicotine induced contractions of isolated intestinal strips by atropine is generally interpreted as indicating that the action of the former drug is mediated by cholinergic neurons of the plexuses Atropine however does not block the stimulant action of nicotine on the intestine of the rabbit[41] or on the isolated muscularis mucosae of the dog[42] Likewise adrenergic blocking agents and antihistaminics fail to prevent the effect of nicotine on these preparations[43] These observations have led to the suggestion that substance P may be the neurohumoral agent involved

Substance P First prepared from alcoholic extracts of brain and the muscular layers of the intestine by von Euler and Gaddum[44] in 1931, substance P has the properties of a polypeptide and, according to recent chromatographic analyses at least two such substances exist[45] *Von Euler[46] proposed that the* spontaneous contractions of the intestine might be due to the release of substance P It may also be the agent responsible for the atropine resistant contractions induced in the stomach of the frog[47] and cow[48] by vagal stimulation The distribution of substance P in the various layers throughout the length of the gastrointestinal tract has been determined in the dog[49] and several other species[50] The results of the two studies are in close agreement and indicate that the highest concentrations regionally occur in the duodenum jejunum colon and rectum The concentration falls progressively along the ileum to the ileocecal valve The layer which showed the greatest amount per gram of tissue was the muscularis mucosae In the dog its concentration there was from threefold to twentyfold more than in the muscularis externa of the corresponding regions Further indirect support is thus provided for the concept that substance P acts as a mediator in the muscularis mucosae Comparable figures for the concentrations of substance P in the gastrointestinal tract of the rabbit would be of considerable interest

Histamine Histamine has been considered as a possible humoral agent of the gastrointestinal tract for both secretory and motor functions It was found in significant concentrations in the mesenteric nerves by von Euler[51] Determinations of its concentration throughout the dog s gastrointestinal tract indicated that like substance P it is most concentrated in the muscularis mucosae[49] There is little direct evidence at present however of its having a neurohumoral function

Enteramine The same might be said of enteramine or 5 hydroxytryptamine a substance which has been isolated from the gastrointestinal tract and other glandular tissues by Erspamer[5] Its structure was first determined by Rapport[53] who identified it as the vasoconstrictor substance of serum In the digestive tract it appears to be concentrated mainly in the glandular mucosa rather than in the muscular layers[54]

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Discussion of the Paper

QUESTION In your estimation what is the function of Peyer s patches?

DOCTOR KOELLE They undoubtedly have some function concerned with immunological reactions I do not believe they play any role with regard to motility

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NORMAL AND SOME ABNORMAL COLONIC MOTOR PATTERNS IN MAN

By Charles F. Code, George R. Wilkinson, Jr., and William G. Sauer
Mayo Foundation, University of Minnesota, and Mayo Clinic, Rochester, Minn.

A broad review of the literature will not be attempted in this discussion. The report will be concerned mainly with the summarization and integration of studies on the colon carried out in our gastrointestinal motility laboratory and previously published.

Methods

Two methods for recording motor activity in the colon have been employed in the laboratory. The first involves the use of balloons[1, 2] and the second the use of a miniature pressure transducer.[3, 8]

The balloons are small (FIGURE 1b). They measure 3 cm. across and 5 cm. in length and when filled but not distended they contain about 35 ml. To minimize the likelihood of the elastic properties of their walls contributing to the pressure recorded, the balloons never contain more than 20 to 25 ml. of water when in place in the bowel.

Tandem balloon systems (FIGURE 1c) have often been placed in the large bowel through colonic stomas.[9, 10] Sometimes in the lower part of the large bowel the two balloons were separated by a greater distance so that one rested well within the pelvic colon and the other within the ampulla of the rectum.[2] The great advantage of the tandem system is that some assessment of the degree of coordination in the motility of adjoining segments of the bowel can be made.

The changes of pressure within the balloons have been recorded by means of glass spoon manometers shown in FIGURE 1a. A rise of pressure in the spoon opens it. This movement is transmitted by the reflection of a beam of light from a mirror mounted on the tip of the spoon to a moving photographic film (FIGURE 2). When the pressure rises in the balloon, the spoon opens and the light beam moves upward on the film. Between the balloon and the spoon an air chamber of about 120 ml. is inserted so that the contractions of the bowel force water from the balloon into the reservoir in precisely the same fashion as they would move the contents of the bowel into adjoining segments.

The tiny electrically operated pressure transducer is mounted in the end of a Sawyer gastric tube (FIGURE 3a and b). A cross section of this little apparatus helps to illustrate its modus operandi (FIGURE 3c). The principle involved is similar to that of the old inductorium used for so many years by physiologists as an electric stimulator. A soft iron core is surrounded by a primary coil carrying a current and a secondary coil in which a current is induced. The strength of the current in the secondary coil is dependent upon the position of the iron core. In the transducer, the position of the soft iron core in turn depends upon the amount of pressure applied to the piston or valvelike structure to which it is attached. The piston is held in place by a rigid spring just like the valves in an automobile engine. The entire unit is housed in a metal cylinder. The piston or valve at the open end of the cylinder is covered by a sheet

DOCTOR JOHN SEED Is the substance bradykinin related to this type of reaction?

DOCTOR KOELLE Whether bradykinin represents a physiologic agent of a breakdown substance obtained only *in vitro* is not known

QUESTION What does serotonin do when applied directly to a piece of isolated bowel?

DOCTOR KOELLE Serotonin causes contraction of the longitudinal muscle of guinea pig ileum which can be blocked by atropine as well as by antihistaminic compounds However it requires greater concentrations of either atropine or antihistamine to block serotonin that it takes to block acetylcholine or histamine, respectively This suggests that serotonin affects both the receptors for acetylcholine and for histamine and by virtue of similarity to adrenalin there is also the possibility that it combines with the adrenergic receptors

DOCTOR H A GORDON (*University of Notre Dame, Notre Dame, Ind*) Do you know of any substances produced by colonic bacteria which may influence or be responsible for colonic motility?

DOCTOR KOELLE In many of the older studies a great deal of the histamine that was reported in various layers of the colon probably resulted from contamination from the lumen as the result of bacterial action I do not think there has been any direct evidence to indicate whether enough of that material can actually penetrate the intestinal wall and bring about changes in motility

DOCTOR GORDON At Notre Dame where I am working with germ free animals, we found that while the tonus is greatly reduced in the cecum of our rats the propulsion does not seem to be reduced and the only variable between our germ free rats and our conventional rats is the presence and absence of bacteria

DOCTOR KOELLE That is an extremely interesting observation It may suggest that histamine and other substances in the lumen actually do exert a controlling influence

DOCTOR QUIGLEY Histamine is destroyed both in the lumen and in the colon and on passage through the lumen is absorbed in the mucosa so that although histamine might have the action indicated in high concentration because of high destruction in the lumen it would not appear so

DOCTOR KOELLE Doctor Quigley has pointed out that although histamine might be absorbed it is destroyed very quickly in the passage from the lumen into the bowel wall Diamine oxidase which destroys it is concentrated in the entire length of the intestine as well as in the liver so that any that was not destroyed at once would be destroyed in the passage through the portal circulation

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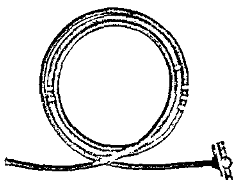
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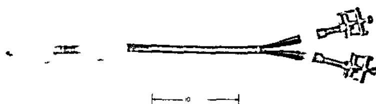
Tandem balloon systems (FIGURE 1c) have often been placed in the large bowel through colonic stomas.[9, 10] Sometimes, in the lower part of the large bowel the two balloons were separated by a greater distance so that one rested well within the pelvic colon and the other within the ampulla of the rectum.[3] The great advantage of the tandem system is that some assessment of the degree of coordination in the motility of adjoining segments of the bowel can be made.

The changes of pressure within the balloons have been recorded by means of glass spoon manometers shown in FIGURE 1a. A rise of pressure in the spoon opens it. This movement is transmitted by the reflection of a beam of light from a mirror mounted on the tip of the spoon to a moving photographic film (FIGURE 2). When the pressure rises in the balloon, the spoon opens and the light beam moves upward on the film. Between the balloon and the spoon an air chamber of about 120 ml. is inserted so that the contractions of the bowel force water from the balloon into the reservoir in precisely the same fashion as they would move the contents of the bowel into adjoining segments.

The tiny electrically operated pressure transducer is mounted in the end of a Sawyer gastric tube (FIGURE 3a and b). A cross section of this little apparatus helps to illustrate its modus operandi (FIGURE 3c). The principle involved is similar to that of the old inductorium used for so many years by physiologists as an electric stimulator. A soft iron core is surrounded by a primary coil carrying a current and a secondary coil in which a current is induced. The strength of the current in the secondary coil is dependent upon the position of the iron core. In the transducer, the position of the soft iron core in turn depends upon the amount of pressure applied to the piston or valvelike structure to which it is attached. The piston is held in place by a rigid spring just like the valves in an automobile engine. The entire unit is housed in a metal cylinder. The piston or valve at the open end of the cylinder is covered by a sheet







FI UR 1 GI poo m om t rs w th m rs tta h d f pt l g t t f pre e ha g Spoons p n w th f p b d B lloo d t b g us d to d t t m til ty in g t o t t nal t t Scal n c t m t rs

of rubber and the other end through which the wire leads leave the unit is held in the Sawyer tube Through connections with a suitable amplifier and a galvanometer pressure changes at the tip of the transducer are recorded on moving photographic paper

The balloon and transducer systems respond almost identically to changes of pressure until a frequency of about 10 pressure waves per minute is reached (FIGURE 4) Then the sluggish balloon system lags although the transducer follows the changes with fidelity Indeed the transducer will follow pressure changes up to 10 cycles per second without erious artifact (FIGURE 5)

The small balloon provides pinpoint detection of motility in a single segment of bowel For the most part it gives a measure of the motor activity in the wall of the bowel surrounding it The record obtained describes the pressure changes in the balloon produced by this motor activity

The transducer provides pinpoint detection of the pressure changes within

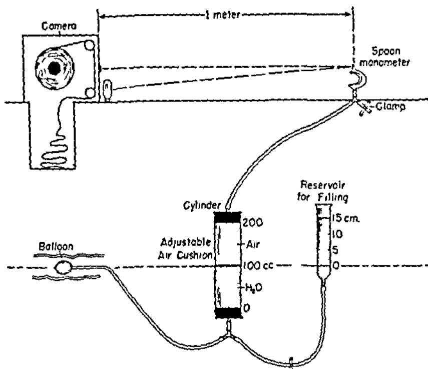
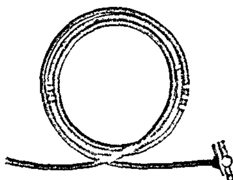


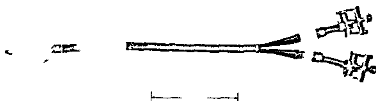
Figure 2 Schematic diagram of apparatus used to record motility of bowel by balloon filled with water

the lumen of the bowel However only motor activity causing a change in intraluminal pressure at the pinpoint where the unit is located will be recorded Conceivably contractions insufficient to raise the pressure in the bowel would go unrecorded or contractions in one segment accompanied by relaxation in adjoining segments might if the transducer lay between them, be undetected

In the colon the photographic record obtained with both systems are composed of definite waves which are the consequence of motor activity in the wall of the bowel Templeton and Lawson[11] first divided the waves recorded from the large bowel of dogs into types I II and III Later Adler Atkinson and Ivy[1] adapted the classification to similar recordings obtained from human being This terminology has been applied in our laboratory to waves recorded from the colon[1 10] and indeed to those recorded throughout the entire gastrointestinal tract[12] The classification has one great advantage—it does not commit the investigator to an interpretation of the mechanical effects of the waves A functional classification of the waves would certainly be preferable but at this stage of knowledge definite assignment of function to each type of wave would be premature and might later be confusing rather than helpful







F UR 1 GI p m met w th m rs tt b d f r pt l gt t t f p r b nge Spoo s p n w th f p b d B ll d t l g d t d t t m t l ty n g tr t t l tr t S l t met

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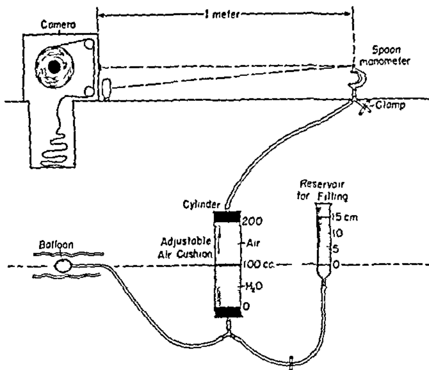
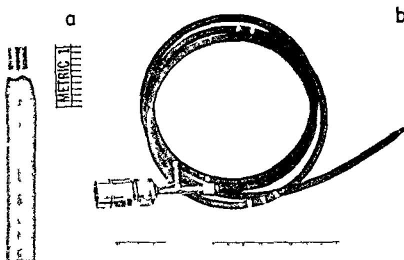


Figure 2 Schematic diagram of apparatus used to record motility of bowel by balloon filled with water

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c

SCHEMATIC DIAGRAM OF MINIATURE PRESSURE TRANSDUCER

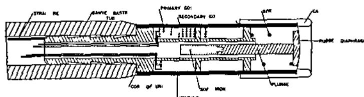
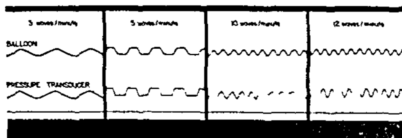


FIGURE 3 a T y l t c p t d m unt d t p f S wy t b b Tr du t b c rry g w e t d n t C t f tr d r

Description of Waves and Analysis of Records

Type I waves (FIGURE 6) are most readily recognized in records obtained with balloons Indeed unless balloon and pressure transducer recordings are made simultaneously it may be difficult to distinguish the type I waves in the trans ducer records Throughout the gastrointestinal tract the type I waves are small simple waves In the colon they are particularly small their amplitude seldom representing a pressure of more than 10 cm of water or their duration more than ten seconds It is often difficult therefore to distinguish them from the disturbances caused by breathing When in rhythmic sequence (that is displaying their basic rhythm) their rate in the pelvic colon is 13 per minute while in the descending colon it may be about one half of this Finally these waves are uncommon in colonic recordings For example in the pelvic colon they usually comprise only about 1 per cent of the record [2] They may how ever occur more often higher in the large bowel Their uncommon occurrence in the records may mean that they are actually present infrequently or it may mean that our pick up units for the recording of motility—balloons or transducer—fail under some circumstances to detect them They are intriguing



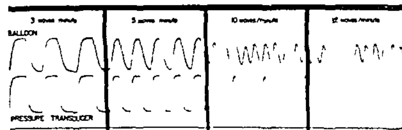


FIGURE 4. Simultaneous responses of balloon and transducer recording systems to changes in pressure at various frequencies. At rates of 10 or more per min the sluggish balloon system fails to follow the pressure changes of the [illegible]. From Code, Hightower and Morlock. Reproduced by kind permission of the authors and of the Editor of the *American Journal of Medicine*.

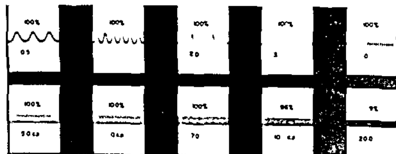


FIGURE 5. Dynamic responses of transducer system to fixed changes of pressure applied at various frequencies. Responses given as percentage of static response to the pressure. Reproduced by kind permission of N. C. Hightower, Jr.

little waves What function are they performing? No data can be offered in answer All are agreed that they are not propulsive Are they due to contractions of the muscularis mucosae and if so which of the function of the colon are they aiding?

Type II waves (FIGURE 1) are also simple waves but they are uniformly of greater duration and almost always of greater amplitude than type I waves

Cms
H_2O
10
0
BALLOON
PNEUMOGRAPH
1 MIN
30
20
TRANSDUCER
PNEUMOGRAPH

FIGURE 6 Type I w v corded f m pel colo of norm l p rso by b lloo a i t d ce method

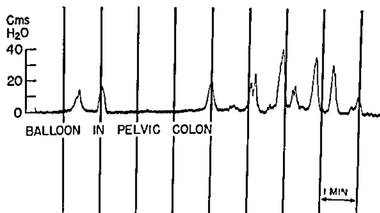
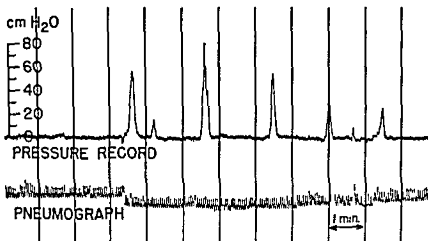


FIGURE 7 Type II wav r cord d by b lloo i pel c c l of n rm l p rs i th f t d st t F m Sp ggs Code B g C t s d H ght w R prod d by k d perm f th t) a d f th Ed t r f *Gast ent logy*



Fi ur 8 Type II wa es rec rded by lect ic pressure transduc in pel l f p rmal person in th fasted tat

As seen in the pelvic colon their duration is commonly one third to one half of a minute and in this location they are detected as satisfactorily though possibly not as frequently, by the pressure transducer as by the balloon (FIGURE 8) The pressures they produce seem least in the lower regions of the colon For example the mean pressure developed by type II waves in the pelvic colon has been found to be about 10 cm of water while in the upper regions of the large bowel the impression has been gained that their mean pressures are two or three times this value

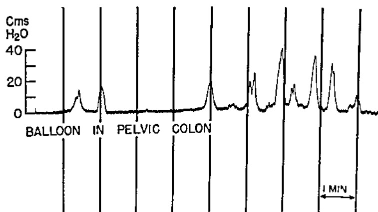
When in rhythmic sequence the frequency of these waves is almost exactly 2 per minute A burst of rhythmic type II waves displaying their basic frequency or rhythm of 2 waves per minute is shown in FIGURE 9

Bursts of type II waves occurring in rhythmic or irregular patterns constitute the main type of activity seen in colonic motility records from normal human beings Indeed in normal persons they generally account for more than 90 per cent of the recorded activity

As a rule these waves are not propulsive In recordings from tandem systems of balloons as illustrated in FIGURE 10 they often occur quite independently in the two records Their occurrence may sometimes be coordinated or more or less simultaneous in the two balloons but whether this is by design or by coincidence and whether it then constitutes an important propulsive component of motor function of the large bowel is very difficult to assess It seems certain that in general these waves do not represent propulsive activity in the lower part of the bowel and that they are not peristaltic contraction rings passing analward along the large bowel Rather they represent slow contractions which migrate very slowly over very short distances The evidence available indicates that they cause the haustra seen in roentgenograms and account for the haustral contractions observed roentgenoscopically by

Cms
H_2O
10
0
BALLOON
PNEUMOGRAPH
1 MIN
30
20
TRANSDUCER
PNEUMOGRAPH

FIGURE 6 Type I w re d d f omp l l n f rm l p rs s by b ll n d t n d e m th d



FI UR 7 Type II w v ec d d by b lloo pel c l f rm l p rs in th f t d tat F m Sp igg Cod B gen C tiss d H ght w Rep od d by k d p rm f th th rs a d f th Ed t of G st enter logy

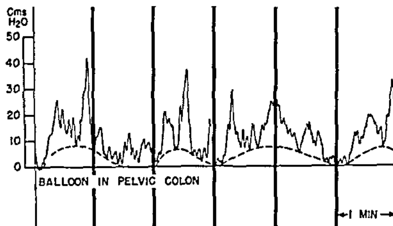


FIGURE 11 Type III wa es repres ted by d tted lines rec ded aft gestion f food, from pel colon f rmal person From Spriggs Code B rg n C rtis and Hightower R produc d by kind permis io f th th rs d f the Ed t f *Gast enter logy*

designate as a type III wave is the base line pressure change from which the other waves arise These base line pressure changes are usually of low amplitude most often being less than 10 cm of water but their duration is long They often last for about a minute and sometimes for many minutes In our experience these waves are not common in records from the colon In the pelvic colon in which region our most detailed studies have been made they were present only about 2 per cent of the total time during which observations were made in normal fasted persons[2] The logical though of course unproved function to assign to these waves is one of aiding absorption by increasing intraluminar pressure

The study of records obtained from patients having ulcerative colitis has necessitated the designation of a fourth type of wave[2, 16] type IV waves They are large simple waves (FIGURE 12) simple in the sense that they have no other components superimposed on them They have clean up-and-down sweeps They are usually represented by a very steep or rapid rise in pressure and a more prolonged decline (FIGURE 13) The pressures attained in the balloons during this type of activity may be considerable pressure up to 100 cm. of water has been recorded

These waves are definitely propulsive When present in the colon adjacent to a colonic stoma material gushes out onto the surface and when obtained in records of activity of the pelvic colon passage of gas or feces is almost always associated. Although the waves are propulsive they apparently are not truly peristaltic They do not represent a ring of contraction which sweeps analward over a number of segments of the large bowel for as Franz Ingelfinger first emphasized to us they occur simultaneously or practically so in both balloons of our tandem system (FIGURES 13 and 14) The waves do not start in the cephalad balloon and pass to the caudad balloon For all practical purposes

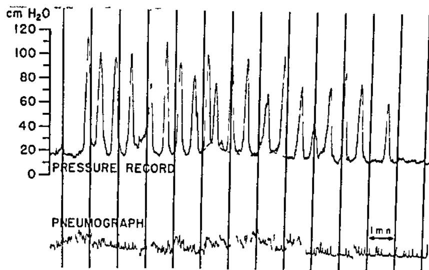


FIGURE 9 Rhythm type II wa d d by el ct c p s re tra sduc in pel c lon f orm I person f ted tate o a d th f rth h rs ft adm n trat n f 80 mgm of D m th d N te bas c hyth m c t of 2 wav pe m t

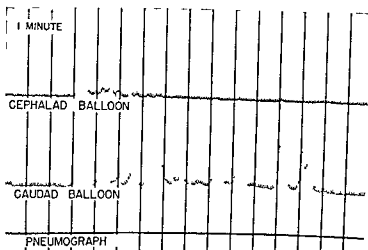
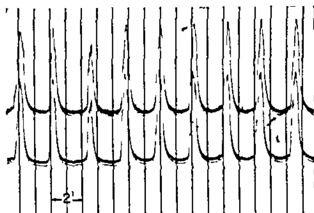


FIGURE 10 Type II w c d d by ta d m b lloo yst m tra rs l th gh c l t m N t th t w m y oc i d pend tly in th b lloo F om H ght w Cod i M h R p od d by k d perm s f the a tho s d f th Ed t f P c ed g f th St ff M t g f th M y Cl

radiologists[14, 15] Their function seems to be one of mixing rather than propel ling They may aid absorption not only by digging into the contents and turn ing it over but also by raising intraluminal pressure

Type III waves (FIGURE 11) are complex They are composed of a change in base line pressure or a change in tonus upon which are superimpo ed type I or type II waves or both The component of the complex which we measure and



F GU 14 Rhythm type IV w f llow g dm t t on f eost gmin Re rd d by t ndem balloon y tem l th ough l tom N t m lta oc rr f w t th b ll o From M M h Cod S d B g n R prod d by k d permi l f th a th rs nd f th Ed t f G f o- *enter logy*

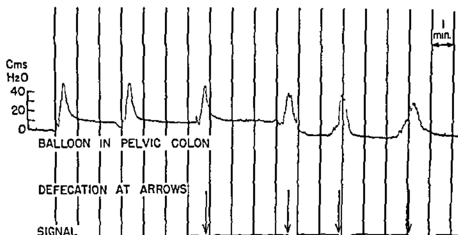
bowel over some distance Holzknecht[17] who originally described the move ments mentioned that the haustra disappeared when they occurred We have never seen a type II wave associated with a type IV wave Holzknecht and others who have confirmed his roentgenoscopic observations also noted that transport of the contents out of the affected area occurred within a few seconds They observed the component of the wave represented by the rapid upsweep of pressure It lasts only a few seconds (FIGURES 12 13 and 14) Once the bowel was emptied of opaque material they would not see the slow decline of pressure which represents relaxation of the bowel (FIGURES 12 and 13)

When these waves occur in rhythmic sequence there is usually one wave every three or four minutes Their maximal rate seems to be one every two minutes This has been recorded quite regularly after administration of neo stigmine[10] Notice in FIGURE 14 the clocklike precision with which these waves occurred simultaneously in the balloons of a tandem system

General Pattern of Motility in Normal Persons

The component parts of colonic motility have just been described Now an attempt must be made to reassemble them in their proper proportions and patterns so that the true general or over all pattern of colonic motility may be visualized It is one thing to dissect or dismantle the complex picture and another to reconstitute it accurately! Our most quantitative data from normal persons have been obtained in the pelvic colon since it is the most accessible portion of the colon in such persons

In FIGURE 15 is shown about one and one third hours of record from a normal subject fasted overnight The first measurement we would make on such a record is the percentage of the period of observation during which activity is present This record shows activity during more than half of the time which is more than usual for normal persons fasted overnight Notice that periods



F OURE 12 Type IV w re o d d aft g st of food from pel col f pat nt h ing l ativ l t Fr m Sp ge Code B g n C rtl d H ght w r R p odu d by k nd perm of the auth rs d of th Ed t r f G t ent logy

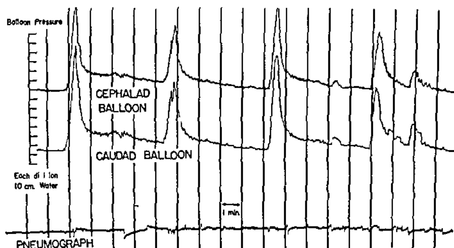
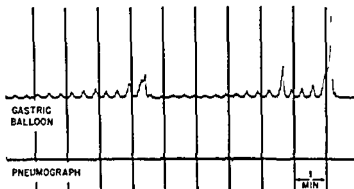


FIGURE 13 Type IV w a r ord d n tra ers lo th gh l toma by t nd m b l system N t sm ltane occurr ce f w th b lloo F om Cod H ghtow d M lock R p od d by kind perm s f the a th rs nd f the Ed tor f the *Amer Jou l f M d*

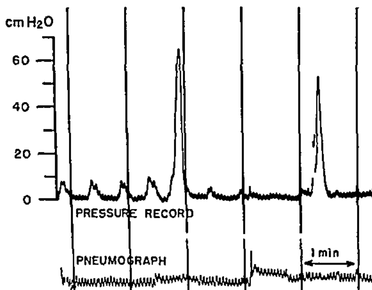
they appear at the same time in both balloons Thus they cannot represent a progressive wave of contraction but rather the simultaneous contraction of the bowel over a number of segments—at least as indicated by our tandem systems over a distance of 12 to 14 cm and perhaps more We have seen this wave only once in tracings from normal persons and that was when the subject defecated just after eating a meal

These waves we believe represent mass movements described many years ago by roentgenologists[1, 21] We submit that they are not peristaltic as was originally suggested, but that they involve the simultaneous contraction of the

Ten such subjects were studied in the laboratory Some estimate of the over all picture could be gained by scanning the 10 records but in our experience such estimates have usually been biased We have therefore been forced to measure accurately the waves seen in the tracings The measurements have allowed the summarization of yards and yards of tracings into a concise set of data compressing what is sometimes a rather complicated and confusing sequence of records into a clear and simple table

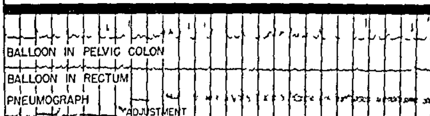


F GURE 16 Antral ga tric mot l ty f rm l pers rec rded by balloon Type II w es occurring tep with type I wa es From Hightow Cod d M h R p od d by k d perm on f th thors and f th Edito f *P oc ed g f th Staff M t g of th M y Cl c*



F gu 17 P l lon m t l ty rd d by pre tra d c f rmal pers f ted t h s Larg type II wa occ rr g in tep w th mall type II w es

MOTILITY IN PELVIC COLON AND RECTUM
FASTING NORMAL SUBJECT



CHANGE IN BALLOON RECORDS EQUAL TO 20 Cms H2O PRESSURE

min

FIGURE 15 O h a d tw ty m t c t s d g f m t l ty n p l c col f m l f t d p rs n F m Sp gg Cod B rg C rt s d H ght R p od d by k d p rm f th uth rs s d of th Ed tor f G s l l l gy

of complete quiescence intervene between the active sessions The activity in the tracing is composed predominantly of the innocent type II mixing waves, the haustral contractions sometimes in rhythmic two per minute pattern A few type I waves are evident but no type III or type IV waves

TABLE 1
MOTILITY OF THE PELVIC COLON IN 10 FASTING NORMAL SUBJECTS

	M m ot m d n w f d ? t type				
	Typ I	Type II	Type III	Type IV	All type
Per cent of observation time present	1 1	36 3	2 3	0	36 6
Mean height mm †	6 8	9 7	5		
Mean duration minutes	0 09	0 4	0 9		
Rate per minute when approximately rhythmic	13	2 0			

Th total pe nt g t ty l l th n th s m f th pe tag t t f th d ff t w f rm b th wa f rm m t m s s p rimpo d th t A d ft t n th r c d of 1 mm respo d t e b lloo p e f 1 cm w t

Ten such subjects were studied in the laboratory Some estimate of the over all picture could be gained by scanning the 10 records but in our experience such estimates have usually been biased We have therefore been forced to measure accurately the waves seen in the tracings The measurements have allowed the summarization of yards and yards of tracings into a concise set of data compressing what is sometimes a rather complicated and confusing sequence of records into a clear and simple table

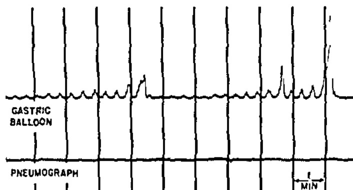


Figure 16 A tral ga t m t l ty f rm l pers n re d d by balloon Type II occu g t p w th type I wa es F m H ght w Cod d M h R prod d by k d perm f th a th rs d f th Ed t f *P oc ed g of th Staff M t g f th M y Cl*

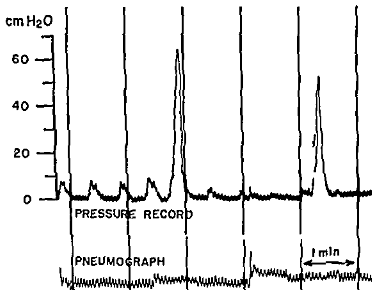


Figure 17 P l l m t l ty o d d by pre t d f m l pers f t d 15 h rs La g type II w oc g t p w th *mall type II w*

An example is presented in TABLE 1 It condenses the records from the 10 normal subjects Some activity was present in the pelvic colon about one third of the time Type I waves were present only about 1 per cent of the time and type III waves about 2 per cent Most of the activity was due to type II waves and no type IV waves were seen The rate of the type I waves, when rhythmic was 13 per minute and that of the type II waves two per minute The duration and amplitude of the waves are also summarized

Similarities with Pattern in the Stomach

Does this pattern of activity resemble that seen anywhere else in the alimentary canal? Yes in normal persons there are some similarities between the activity recorded from the pelvic colon and that seen in the antrum of the stomach

GASTRIC BALLOON
PNEUMOGRAPH
BASE LINE
1 MIN

FIGURE 18 Rhythmic type II w d d by b ll f m trum f tom h f rm l pe F om H ght wer a d Cod R p od d by k d p rm ion f th th rs d f th Ed t of *P ed g f th St ff M et gs of th M yo Cl c*

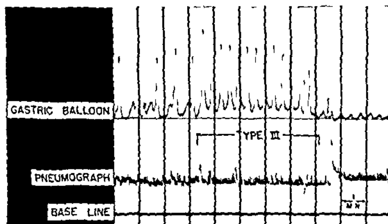
cm H_2O
70
50
30
10
PRESSURE RECORD
PNEUMOGRAPH
1 min

FIGURE 19 Rhythmic typ II w es pel l f n rm l p rs tw d e-f th h rs ft b- cuta us dm trat f 0 2 mgm f m rphin lf t per k l g m f body w ght R d d by l t pre t d r

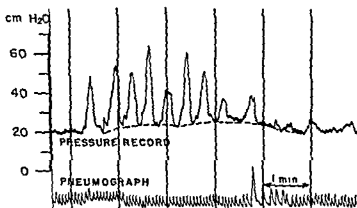
First balloons in the pelvic colon or in the antrum of the stomach of normal persons who have fasted overnight record activity during about the same proportion of the time 36[2] and 38[22] per cent respectively

Second in the antrum type I waves often occur in rhythmic sequence and when type II waves intervene in such a sequence they usually appear in precisely the position a type I wave would have been expected[11] In other words the type II waves occur as if in step with the rhythm (FIGURE 16) A similar sequence in the colon is illustrated in FIGURE 17, a large type II wave occurring *exactly in step with its smaller predecessors!*

Third in the stomach, type II waves are present in a rhythmic sequence quite often and then they display their basic rhythm of 3 waves per minute



Fi u 20 Type III w e w th pe mpo d hythm type II wa es d d by balloon f om antrum f st m h f rm l pers n



F URE 21 Type III w th s pe impo d ythm type II w ec rded by lect t sd f m pel i l f rm l pers tw ty min t ft dm trat on f 0 2 mgm f m rphin ulf t pe k l gram f body w ight

or a twenty second rhythm[22] They then have the appearance seen in FIGURE 18 Without the legend, could you differentiate FIGURE 18 from FIGURE 19? In FIGURE 19 rhythmic type II waves, occurring with clocklike precision are being recorded from the pelvic colon and the only difference in the records seems that the rate is 2 rather than 3 per minute

Finally in the antrum, a period of activity may terminate with a burst of rhythmic type II waves superimposed on a rise of base line pressure—a type III wave[2] (FIGURE 20) This may also occur in the pelvic colon (FIGURE 21)

In these records type II waves from the two areas seem very similar In the stomach, they are the hunger contractions in the colon the haustral contractions In the stomach they are propulsive peristaltic rings sweeping for varying distances over the antrum In the colon they have lost their mobility and are more or less fixed Could this loss of propulsive action in the colon be associated with the loss of external longitudinal muscle fibers and the associated disruption of nerves? Are not these waves really close relatives?

Alterations in the Pattern of Motility in the Pelvic Colon Caused by Ulcerative Colitis

Finally some of the changes that may occur in the pattern of colonic motility with disease may be illustrated by summarizing the results obtained in a study of patients having ulcerative colitis[2]

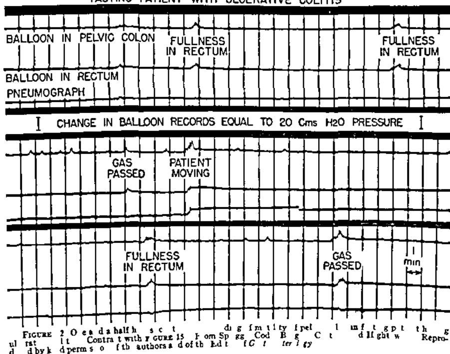


FIGURE 2? O e a d a half h s c t di g f m t l ty f pel l mf t g p t t h g ul rat l t Contra t with FIGURE 15 F om Sp gg Cod B g C t d Il ght w Repro- d d by k d perm s o f th authors a d of th Ed t f G t ter l gy

TABLE 2
MOTILITY OF THE IELVIC COLON

	P r e t of b rvat t m d g h h w s w re p se t				
	Type I	Type II	Type III	Type IV	All types
10 normal subjects	1 1	36 3	2 3	0	36 6
10 patients having ulcerative colitis	2 9	9 8	0	8 1	19 0
Difference	1 8 (p > 0 9)	26 5 (p < 0 01)	2 3 (p < 0 05)	8 1 (p < 0 05)	17 6 (p < 0 05)

First the general over all picture is illustrated in a tracing from a patient in a very active phase of the disease (FIGURE 22) Notice in the figure the over all reduction in motility also that there are no really respectable type II waves (the haustra are gone but there are a considerable number of type IV waves) feeble indeed but strong enough to force material analward

A summarization of the records obtained in 10 patients having the disease is accomplished in TABLE 2 Over all activity was reduced It is down to 19 per cent of the time of observation The innocent type II waves have been cut to one fourth of their normal incidence and in their place the dangerous propulsive type IV waves have emerged It may be concluded from these motility records that patients who have chronic ulcerative colitis do not actually have too much motility but rather that the over all motility is decreased In these patients the gears for regulating motility have not been properly set The mixing and absorption inducing type II and III waves have been drastically reduced or have disappeared and in their place has emerged the mighty mass movement the type IV wave These patients do not need antispasmodic drugs for they have already lost their tone waves nor do they need *cholinergic* blocking agents or drugs which stop or decrease motility They have too little motility as it is! The therapy needed for this type of patient would increase the motility and at the same time coordinate the controlling mechanism, so that a more normal proportion of innocent type II and III mixing and absorption inducing waves will be present and the dangerous type IV waves will be reduced in frequency to their proper incidence of three or four daily

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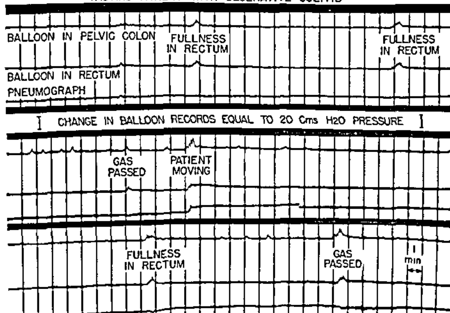


FIGURE 22. One d h lf h urs tin d g f m t l ty f pel l f t g p t th g ul erat i t Co tra t w th URE 15 F om Sp gg Cod B g C rtiss a d Hightow Rep o- d c d by k d permiss f th th d f the E l t f G l l l gy

study and it would be an excellent one Our subjects all had very regular bowel habits They seem to be able to train themselves very well and in fact usually have already evacuated their bowels before arriving at the laboratory We have not done the study with the bowel being stimulated by balloon or by giving additional material to the colon

QUESTION What about the spasmodic colons?

DOCTOR CODE The question is whether we have made a study and obtained records in patients with a spastic colon or a colon showing spasms We have not done so

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Discussion of the Paper

Question Were any steps taken to abolish the pain occurring with the movements of ulcerative colitis?

Doctor Code No

Chairman Almy Is there any correlation of pain with type IV contractions?

Doctor Code The only correlation with pain that we have observed is in normal individuals that is those with colon motor activity When we gave morphine or prostigmine they complained of cramps associated with pronounced increases in activity but we did not have balloons in place so we are unable to state in precise terms just what type of activity caused the cramp We have had people with pronounced activity but they were not suffering from cramps I am inclined to feel that the concept of the occurrence of discoordination presented by others but not measured by us may account for the cramp but we have no data on it

Doctor Ingelfinger In obtaining your pressure units did you ever introduce any material or did you take the rectum just as it was?

Doctor Code We did not introduce any material That is a separate

study and it would be an excellent one Our subjects all had very regular bowel habits They seem to be able to train themselves very well and in fact usually have already evacuated their bowels before arriving at the laboratory We have not done the study with the bowel being stimulated by balloon or by giving additional material to the colon

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THE ACTION OF AUTONOMIC DRUGS UPON THE HUMAN COLON

By Fred Kern Jr Thomas P Almy, and Marvin H Sleisenger
Department of Preventive Medicine and Public Health School of Medicine University of Colorado Denver Colo and Department of Medicine Cornell University Medical College New York N Y

Knowledge of the effect of autonomic nervous system stimulation and autonomic drugs on the gastrointestinal tract of man is scanty Most of the available information is inferred from conflicting data derived from *in vitro* experiments and from a variety of experimental procedures performed on many different types of animal preparations In general, the end organs observed have been the small intestine and stomach rarely the colon Further the anatomical and functional organization of the colon of the commonly used animals differs considerably from that of man s colon When studying physiology and pharmacology in man one must be concerned not only with contraction or relaxation of the individual muscle fiber, but also with the relationship of the parts to the behavior of the entire organism

These relationships are extremely important in attempting to understand the motor activity of the colon Most evidence indicates that all such activity of the colon is stimulated by the parasympathetic portion of the autonomic nervous system How then can one explain the varying patterns of muscular activity spontaneously occurring in the colon of man? Patterns that are apparently associated with increased motility give rise to diarrhea in one instance and to constipation in the other [1]

Method of Study

Since the motility of the sigmoid colon is thought to be pertinent to the pathogenesis of diarrhea and constipation our study has been limited to a large extent, to the observation of this portion of the bowel A condom rubber balloon about 15 cm long is tied to a reinforced French 14 or 16 Levine tube and threaded through a proctoscope into the sigmoid The tube is then connected to a sensitive air water system which is inflated to approximately the same pressure each time Changes in pressure are recorded on a slowly moving drum This method of recording sigmoid motility has previously been described in detail [2] Our subjects are either normal volunteers patients with functional bowel disorders or patients with unrelated diseases They are brought to the laboratory after a six to a 16 hour fast and about two or three hours after a saline enema All drugs have been administered only after a 30 to 60 minute control observation

In several hundred recordings of sigmoid motility during one to three hour control periods the pattern of the tracings has been a nearly continuous succession of irregular and complex waves with interruption of activity seldom longer than five minutes at a time Type I and II contractions as described by Templeton and Lawson[3] and Atkinson Adler and Ivy[4] can easily be defined but type III contractions occur less frequently These contractions of

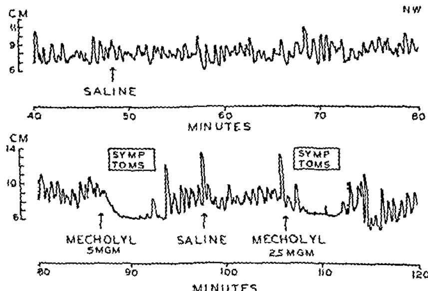
the distal colon are not propulsive [3,4] In patients with chronic ulcerative colitis however a different type of sigmoid contraction called type IV [4] is definitely associated with propulsive activity

Acetyl Beta Methylcholine and Acetylcholine

The first cholinergic drug studied was *acetyl beta methylcholine chloride* or *methacholine chloride* [5] This choline ester lacks the nicotinic or synaptic action of acetylcholine having only muscarinic action Since it is hydrolyzed by cholinesterase *more slowly than acetylcholine* it was *administered* subcutaneously The drug was given 49 times to 24 subjects in amounts ranging from 2 5 to 10 mgm All injections were preceded by the hypodermic injection of saline After the methacholine was administered the blood pressure and pulse were recorded every one or two minutes until they had returned to control levels Observations were made simultaneously of other systemic effects such as flushing sweating salivation dyspnea and lacrimation

Results In 20 of these 49 experiments marked diminution or complete abolition of wavelike motility in the sigmoid accompanied the usually observed systemic effects of the drug (FIGURE 1) In no instance did methacholine produce augmentation of sigmoid motility In six experiments the results were inconclusive In 23 experiments there was no change in sigmoid activity after methacholine

Acetylcholine has been administered by continuous intravenous infusion 21 times to 18 healthy volunteer subjects [6] A saline infusion was always begun during the control period and the acetylcholine solution containing 5 or 10



[illegible]

mgm per cc, was introduced by means of a three way stop cock Each infusion of the drug lasted 10 to 15 minutes The rate of flow was increased slowly and stepwise to the limit of the patient's tolerance, where it was then maintained The patient's tolerance was defined as the amount of drug per minute, which caused persistent moderate respiratory distress (a sensation of tightness in the chest and restricted respirations) If this amount were exceeded the subject often had uncontrollable coughing or nausea In these experiments also blood pressure and pulse were recorded each minute during the infusion and the subjects were carefully observed for salivation, sweating lacrimation, flushing and respiratory distress Since each of the systemic effects was variable in degree from time to time during the infusion no single one was considered a reliable guide

Results In 15 of the 21 experiments there was diminution or complete abolition of wavelike contractions of the sigmoid (FIGURE 2) This change in sigmoid motility became apparent only when the rate of infusion was such that there was continued respiratory distress marked flush of the face salivation and sweating Abdominal cramps or a desire to defecate or urinate were rarely observed That this could be repeated in the same individual is shown in FIGURE 3 In all experiments termination of the infusion was followed by a prompt return to the previous pattern of sigmoid motility All signs and symptoms of acetylcholine effect disappeared within one or two minutes In these experiments the blood pressure fluctuated widely during the infusion There was a rise in blood pressure in almost all subjects followed by a fall below the control level in 13 Often there was a fall in the diastolic pressure

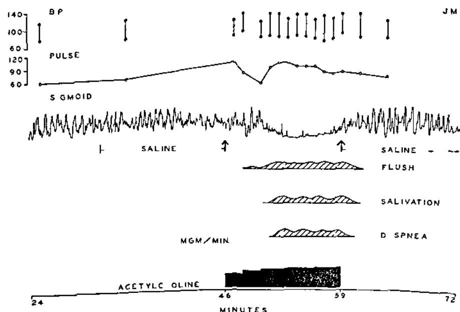
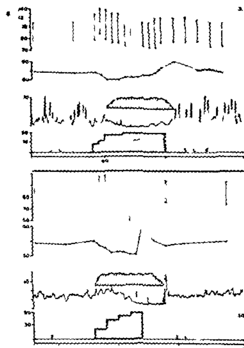


FIGURE 2 Typ l h g s th mot l ty f th gm d l d g f f tyl h l

only with an increase in the pulse pressure The amount of acetylcholine required to produce these effects varied from 20 to 120 mgm per minute with an average of 72 The effective amount appeared to be independent of the weight of the individual It should be emphasized that there was no effect upon the colon until marked systemic effects were present

In four experiments the acetylcholine had no detectable effect upon the motility tracing In two experiments there was a definite increase in activity of the sigmoid In these six experiments the systemic signs of an effective infusion were no different than in the others

Comment It is apparent from these studies that in most normal individuals acetylcholine causes a marked decrease in the wavelike contractions of the sigmoid colon It is possible that this may be effected by either of the two modes of action of acetylcholine It may be a direct effect upon the smooth muscle of the colon or it may reflect the nicotinic action of acetylcholine that is, the result of stimulation of sympathetic ganglia including the adrenal medulla, with the release of epinephrine There is considerable evidence to indicate that this is the result of the direct muscle effect First the effect on sigmoid motility always occurred at a time when there was ample evidence of stimulation of end organs (sweat glands and salivary glands) which respond



F ure 3 Ac tyl h l f es n tion in gm d m t l ty tw th sam bject Th tw xpe ime ts 3 w ek part

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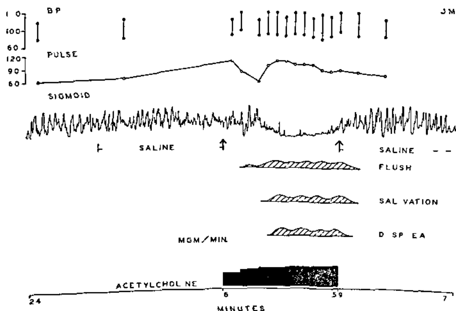


FIGURE 2 Typ l h g s th m t l ty f th gm d l d g f f tyl h l

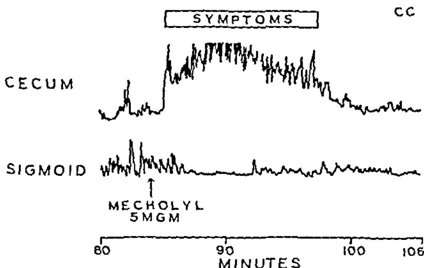
experiments the administration of these agents in the usual manner was followed by *vigorous contraction of the cecum and the ascending colon, while the* sigmoid and descending colon widened and shortened (FIGURE 6)

Other Cholinergic Drugs

Urecholine® a choline ester which is not hydrolyzed by cholinesterase has *prolonged effects after subcutaneous administration* Twenty *subjects were* given 2 5 to 5 0 mgm of this agent with a resulting increase in amplitude of sigmoid contractions usually persisting from 15 to 30 minutes (FIGURE 7) The usual systemic effects of cholinergic stimulation are less marked with urecholine than with acetylcholine or methacholine

Carbaminoylcholine or doryl® is a potent parasympathomimetic agent which is not hydrolyzed by cholinesterase and has a potent nicotinic action Given subcutaneously to three subjects 0 25 mgm of this drug produced an augmentation of sigmoid motility similar to that produced by urecholine in two of them

Physostigmine has been administered subcutaneously to forty subjects In the thirteen experiments in which one mgm or less was used there was slight effect upon sigmoid motility in three In the other experiments the amount of drug varied between 1 5 and 3 0 mgm affecting sigmoid contractions in 21 out of 27 subjects There was a slight to moderate increase in amplitude of contractions (FIGURE 8) lasting from 12 to 25 minutes There was no propulsive activity In tandem balloon tracings with both balloons in the sigmoid the contractions occurred simultaneously No type IV waves were noted Nausea and vomiting occurred frequently with the larger amounts of physostigmine often requiring atropine or banthine for relief



F cr 5 5 m lta r cd g of ontra t on f th um d gm d lon show g th coo dinat tion f m th h lin

only to cholinergic influences Vasodilatation and bronchospasm are also the result of cholinergic stimulation Second it is well established that metha choline, which has an effect similar to acetyl choline on sigmoid motility, does not possess nicotinic action but only direct muscarinic effect Third, it has long been known that atropine blocks only the muscarinic or smooth muscle stimu lating action of acetylcholine or methacholine It does not inhibit the nicotinic effect If the effect of methacholine were direct on the muscle it should there fore be blocked by atropine

In six subjects in whom methacholine produced abolition of sigmoid con tractions the methacholine was followed by the intravenous administration of 0 6 to 1 0 mgm of atropine sulphate This caused only a brief interruption of contractions When the previous pattern had returned, the same or a larger amount of methacholine was again administered, and its effect upon sigmoid motility was blocked in each instance (FIGURE 4)

What is the effect of acetylcholine or methacholine on other portions of the colon? In a patient with a transverse colostomy simultaneous motility trac ings were obtained from the cecum and the sigmoid colon (FIGURE 5) When 5 mgm of methacholine were administered subcutaneously there was a pro nounced augmentation of cecal activity and cessation of motility of the sigmoid These observations were extended by studying fluoroscopically the effects of methacholine and of acetylcholine upon the barium filled colon In 7 of 11

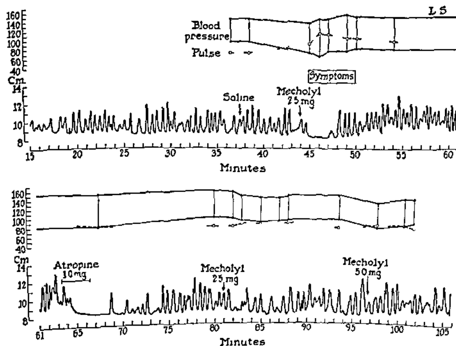
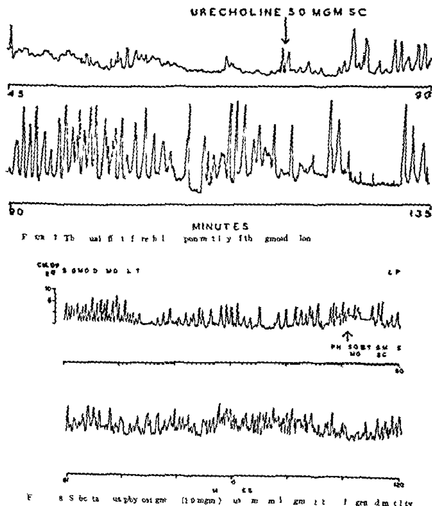


FIGURE 4 M tha h l e f ls to ff ts gm d cont t ft t o t p

selective augmentation of the existing pattern of sigmoid contractions This may be due to slow absorption of the subcutaneously injected drug

The sigmoid response to methacholine and acetylcholine reflects yet another mechanism It has been repeatedly observed in man and animals that during mass peristalsis which is the only known propulsive activity of the colon the proximal colon contracts and empties itself into the distal which shortens and becomes a receptive semirigid tube During this process circular muscle contractions are absent in the sigmoid It appears from these experiments *that the injection of acetylcholine or methacholine stimulates colonic behavior* similar to mass movement which is responsible for normal propulsion These



F ... 7 Th ... ual ff t f re b l ... pon m t l y f th ... gmoid ... lon

F ... 8 S bc ta ... us phy ost gm ... (1 0 mgm) ... u m m l ... gm ... t t ... f gen d m t l ty

BEFORE





AFTER



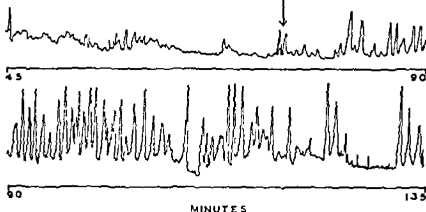


FIGURE 6 Roe tg l g ppe ra f th ght d l ft po t f th l b f d n m t ft th bc t dm istrat n f 5 mgm f m th h lin

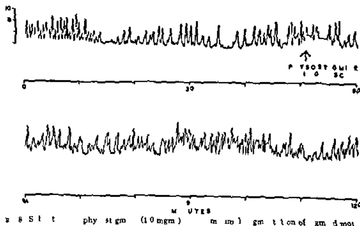
Comment It is thus clear that the effect of physostigmine urecholine and doryl upon the sigmoid is the converse of the effect of acetylcholine and methacholine It appears at first glance that these observations are contradictory but if one examines what is known of the behavior of the colon a tentative explanation can be suggested It is well established that the great majority of contractions of the colon are not propulsive they are simply segmenting circular contractions The effect of physostigmine was therefore anticipated as the only proven action of this drug is the temporary inactivation of cholinesterase thereby allowing each individual neural impulse to the colon to be more effective It is therefore reasonable that the administration of these moderate amounts of physostigmine should permit each circular muscle contraction to become more forceful Doryl and urecholine had a similar effect on the sigmoid but through a different mechanism They appeared to produce a non

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F ta 7 Th ual ff t f y h l po m t l ty f th gm d c l



M UTES
Fı g 8 S t t phy st gm (1 0 mgm) m mo l gm t t on of gm d mot y

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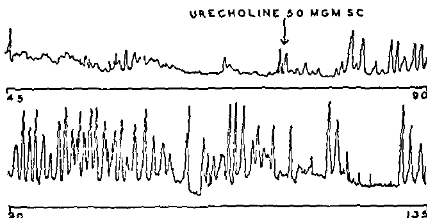


FIG a 6 R tg l g pp e f th r ght d l ft p t n f th l b f d fi m t ft
th b t dm t t f 5 mgm f m th h l

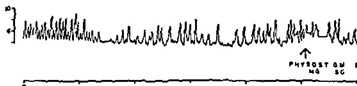
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Fi u e 7 Th ual ffe t of h l pa m t l ly of th gm d colon





Fi u 8 S b t n ou phy ostigr (1 0 mgm) u min m l gm nt t on f sigmo d mot l ty

drugs overwhelm the usual rhythmic circular muscle contractions of the sigmoid They reproduce the pattern of contractions of the colon which occur spontaneously during defecation during mass peristalsis and during functional diarrhea [7]

It is perhaps significant that this pattern of response occurs only with the drugs that are readily destroyed by cholinesterase and which have to be given in large amounts to produce a powerful but short lived effect The other agents physostigmine urecholine and doryl are not destroyed by cholinesterase and therefore must be administered in smaller effective amounts because of their sustained action Were it possible to administer them with safety in amounts large enough to cause parasympathomimetic responses equal in intensity to those produced by acetylcholine and methacholine it is believed that they would produce similar changes in the pattern of sigmoid motility

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Discussion of the Paper

DOCTOR KOELLE Doctor Kern I do not think that the possibility that acetylcholine or methylcholine might be acting by the nicotinic acid mechanism has been fully explored Have you made any studies with hexamethonium to see how that would affect all the responses and to provide the basis of differentiation of acetylcholine and methylcholine with the enteramine?

DOCTOR KERN No we have not

DOCTOR WILLIAM J GRACE (*Cornell University Medical College New York N Y*) Have you ever seen an increase in the base line or frequency of contractions following methylcholine?

DOCTOR KERN No We have observed no such increase during 49 experiments

THE ROENTGENOLOGICAL ASPECTS OF THE NORMAL AND ABNORMAL COLON

By Sydney Weintraub
Cornell University Medical College New York N Y

The visualization of the colon radiographically can be accomplished by the oral method or by means of a barium enema

Oral method After drinking the barium mixture (four ounces of barium sulphate and four ounces of water or normal saline by volume) films are taken at intervals of 3 6 24 and 48 hours This method is one which we rarely use because of the following disadvantages first the colon is not filled completely hence there are areas of nonvisualization Second the contents of the colon cannot be displaced by palpation and the mucosa is not delineated A neoplasm can be easily overlooked Third the transit time of the barium mixture cannot be judged accurately because it depends on the vehicle used to suspend the barium sulphate Weintraub and Williams[4] gave a barium and water mixture to 107 patients who had no organic lesion of the gastrointestinal tract and found that in 22 per cent the head of the column reached the cecum in one hour In a similar group of 114 patients who received a barium and isotonic saline mixture the head of the column reached the cecum in one hour in 54 per cent It is apparent that the normal saline mixture advances through the small intestines almost two and one half times faster than the barium and water suspension

The rate of advance of the barium column is also dependent on the state of hydration of the individual If dehydration is present the barium collects in discrete masses in both the small and large bowel and the transit time will be prolonged as much as 72 hours with the added danger of a fecal impaction

The barium enema Although this method of examining the colon is not entirely ideal nevertheless it has many advantages over the oral procedure With its use a high degree of accuracy has been achieved in the diagnosis of tumors and inflammatory lesions of the colon During the fluoroscopic observation, pressure can be applied to delineate the mucosa and to elicit tenderness In addition the ileocecal valve the terminal portion of the ileum and the appendix can be studied with thoroughness In estimating the functional behavior of the colon one should keep in mind that the patient has taken a cathartic and has received enemata so that there may be varying degrees of irritability and congestion of the mucus membrane Women and children tolerate the procedure better than the male adult The colon in the latter may be so sensitive that the examination cannot be completed even though there is no clinical evidence of organic or functional disease

Anatomy The normal colon is widest at the cecum and diminishes in caliber caudally the narrowest portion being the sigmoid and then it widens again at the rectum There are three bands of smooth muscle which run longitudinally along the surface of the colon They are spaced at equal distance apart and the tonic contractions of these bands produce the haustrations or sacculations of the resting colon These sacculations are largest in the cecum and

drugs overwhelm the usual rhythmic circular muscle contractions of the sigmoid They reproduce the pattern of contractions of the colon which occur spontaneously during defecation during mass peristalsis and during functional diarrhea [7]

It is perhaps significant that this pattern of response occurs only with the drugs that are readily destroyed by cholinesterase and which have to be given in large amounts to produce a powerful but short lived effect The other agents physostigmine urecholine, and doryl are not destroyed by cholinesterase and therefore must be administered in smaller effective amounts because of their sustained action Were it possible to administer them with safety in amounts large enough to cause parasympathomimetic responses equal in intensity to those produced by acetylcholine and methacholine it is believed that they would produce similar changes in the pattern of sigmoid motility

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Discussion of the Paper

Doctor Koelle Doctor Kern I do not think that the possibility that acetylcholine or methylcholine might be acting by the nicotinic acid mechanism has been fully explored Have you made any studies with hexamethonium to see how that would affect all the responses and to provide the basis of differentiation of acetylcholine and methylcholine with the enteramine?

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Normally it is fairly constant in position hugging the left diaphragmatic cupola Its descent toward the iliac crest is an index of ptosis The right colon is so variable in position that only gross displacement downward is of importance

There are numerous congenital anomalies in the position of the various segments of the colon As a rule they do not produce any symptoms Owing to the failure of the cecum to rotate or descend, it may lie beneath the liver or in the left lower quadrant The patient should be informed of this situation because without this knowledge an attack of acute appendicitis would be very difficult to diagnose

Occasionally the mesentery of the cecum or sigmoid which normally is very short may be abnormally lengthened and may be responsible for a volvulus of the segments resulting in acute or chronic intermittent obstruction

To study the functional behavior of the colon continuous fluoroscopic observation is essential The barium is introduced slowly and at minimal pressure The rectum is dilated very gradually There may be considerable delay at the rectosigmoid junction because of spasm or because of a sharp angulation at this point The sigmoid is the most sensitive and the most irritable part of the bowel and to a lesser degree of the descending colon There is also a delay at the splenic and hepatic flexures The flow is helped by turning the patient from side to side so that the gravity is favorable

Spasm of the sigmoid is encountered in most of the functional disorders of the colon such as chronic constipation chronic spastic colitis and mucous colitis It is also present in the inflammatory lesions such as diverticulitis and ulcerative colitides The descending colon may be involved in all of the abnormalities mentioned above

Normally the right colon shows little evidence of irritability and no activity can be elicited in spite of vigorous massage In the presence of inflammation however the cecum will appear spastic and irritable and at times the contractions will be deep and vigorous resulting in filling and emptying of the cecum at intervals—the so-called systole and diastole of the cecum The lesions most common in this area are ileocecal tuberculosis amebiasis regional colitis and appendical abscess

Chronic constipation The textbooks speak of the atonic and spastic types In our experience it is rare to see an atonic colon and many of these are not responsible for any abnormal function of the bowel The spastic colon is by far the most prevalent type and the spasm is usually noted in the sigmoid and descending colon Sudden change in bowel function is often noted in patients in the fifth sixth and seventh decades who have developed diverticulitis of the sigmoid colon

There are many patients however whose main complaint is chronic constipation not relieved by all the numerous advertised remedies who show radiographically a normal colon This calls to mind my experience with a friend a physician about 45 years of age During his stay in the Army in the last war he would have an evacuation once in 7 to 10 days He was very active mentally and physically and never had any complaint As far back as he can remember he rarely had a bowel movement more than twice a week

ascending colon, most regularly formed in the transverse colon where they may be literally geometrical, and gradually disappear as the sigmoid is reached In our experience, the haustrations are usually absent in the descending and sigmoid portions of the normal colon

Movements of the colon

(1) *Haustral churning* This consists of slow alterations in the degree of the haustrations These movements are too slow to be detected fluoroscopically but can be seen in serial radiographs In regard to this point, Grace, Wolf and Wolff made the following interesting observation when studying the exposed human colon The most frequent movement observed was a localized circular constriction usually involving less than 25 mm of the exposed segment of colon occurring most often near the cecum but also involving other areas The constriction began slowly, reached its peak in 30 seconds and gradually disappeared over a period of 60 seconds This type of constriction was often deep enough to divide the exposed bowel into two parts It seems likely that these isolated circular contractions are manifested on X rays as haustrations' The sacculations retain the fecal material for the purpose of dehydration In certain inflammatory diseases of the colon such as tuberculous colitis and nonspecific ulcerative colitis the haustrations are irregular in size contour, and distribution or they may be completely absent

(2) *Mass movement* The sequence of events is as follows the haustral contractions over a considerable segment of the transverse colon disappear The barium shadow has a ribbonlike appearance This change occurs in two to three seconds At the same time a constriction is noted in the proximal portion of the transverse colon proximal to the fecal mass Barclay[3] has stressed the importance of this constriction which he terms the point d appui (fulcrum) and is of the opinion that on its competency depends the successful transference of the fecal mass along the colon This constriction really marks the starting point of the strong peristaltic wave which sweeps the colonic contents toward the rectum The whole process is over in ten to twenty seconds The mass movement may be arrested for a few moments in the sigmoid and then continued until the fecal mass is in the rectum A few seconds after the reflex is completed the haustral contractions reappear and as Barclay so aptly words it The general picture of still life is restored The mass movement was first described radiographically by Holzknecht in 1909 also by Cole[1] in 1934 Mass movements are frequently observed fluoroscopically during the administration of a barium enema They can start in any portion of the colon but evidence of distress is noted only when the mass reaches the sigmoid

The length of the colon varies considerably in normal individuals Redundant loops are commonly seen in the sigmoid and at the flexures There is no correlation as a rule between a long redundant colon and constipation The position of the colon also varies greatly in normal individuals A low position of the viscera is normal in individuals of hyposthenic habitus The transverse colon is often in the form of a dependent loop dipping into the pelvis The position of the splenic flexure is the best gauge for judging coloptosis

PANEL DISCUSSION

QUESTION I was interested in what Doctor Weintraub said about the relative absence of haustrations in the sigmoid We all know that to be true Most of the studies on sigmoid motility or many of them have been made in the pelvic colon where considerable type II activity has been demonstrated Such activity is supposed to be the cause of the haustral appearance and yet occurs where radiologically there appears to be the least haustration Is there any possible explanation for that?

DOCTOR CODE I think the point is well taken in our experience but it is not enough to submit to mathematical examination The type II contractions are much more plentiful They are in the upper regions of the colon Of type II we only have an average total activity of 36 per cent in the pelvic colon In the higher regions of the bowel we notice a higher total activity percentage when present I have not observed enough normal bowels that had a colostomy in those regions to present any really mathematical summary of the data but they give the impression that there is more activity and that the amplitude of haustral or type II contractions is much greater as for example in the transverse colon That fits perfectly with the radiological evidence Those in the lower end of the colon apparently are relatively feeble Their average height is only 10 cm of water and they would not show up very well radiographically

DOCTOR WEINTRAUB Many physicians are surprised when they ee how smooth the descending sigmoid colon is and jump to the conclusion that this is an early ulcerative colitis They have to be convinced that it is the normal and not the abnormal condition

CHAIRMAN ALMY Could I ask a corollary to this question? Are haustrations evidences of activity or not? I have startled our students from time to time by asking them to remember that the colon they found in the cadaver was haustrated Is the colon just too long for itself or does haustration represent uncoordinated circular muscle contraction?

DOCTOR QUIGLEY It could be attributed to the fact that the colon in normal length is shorter than would be the case if it were an entirely smooth tube If the colon were contracted at all it would be forced to form sacculations

DOCTOR CODE The haustra apparently have all the appearance of being active contractions Doctor Quigley mentioned that they can be caused by the shortening of the strings of the sac so that sacculations are produced and I agree that that is one of the effects It looks as if that may be involved in the type II contractions but it is hard to conceive of a really good annular ring being a fold of mucosa With that viewpoint I am in complete agreement and having watched one large bowel through the skin it looked to me very much like contractions It was also mentioned that the contractions seen by Doctor Wolf and his associates on the exposed colon appeared like a ring of contractions In a previous paper it was said that this was a haustral contraction and I agree with that I don t think they are only the pulling of the sac strings

He never had taken a cathartic He probably was fortunate that his father was a doctor and thereby profited from the neglect so prevalent in doctor's families Two years ago he entered the hospital for a minor operation I persuaded him for the sake of scientific curiosity to have a barium enema Much to our surprise his colon was normal in every respect All of which reminds me of a definition of chronic constipation by an author whose name I cannot recall "It is the colonic manifestation of a psychoneurosis"

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just a matter of getting out the hypertrophied portion so probably the same attitude depends on presence that originally did not depend on other constituents of the tissues As far as the levels are concerned under normal or pathological conditions I am not aware of any correlations other than just this minor one but pharmacologically one can quite well correlate activity with nonspecific cholinesterase activity that is as we inhibit nonspecific cholinesterase with contrasting ganglia we see a definite increase in transmission which could be by acetylcholine or other choline ester and when you inhibit specific cholinesterase pharmacologically it is still more prominent

CHAIRMAN ALMY In the blood or tissue?

DOCTOR KOELLE In the tissue I don t know of any relationship between the blood cholinesterase and physiological activity as such

DOCTOR INGELFINGER I should like to ask Doctor Koelle if he means that the bacterial action would not produce any irritant substances to motility or that bacterial action would not produce agents that he recognized in human pharmacology?

DOCTOR KOELLE The big question is the one that Doctor Quigley dwelt on i e whether enough of those things will be absorbed to produce local changes in motility

DOCTOR INGELFINGER It has often been said in the literature that fatty acids are direct stimulants of colonic motility Do you have any feeling on that statement?

DOCTOR KOELLE It takes extremely high concentrations of them in order to show it Again I don t know of any specific evidence that those that are produced by the bacterial flora of the colon would actually bring that about It was an interesting point to bring out

DOCTOR INGELFINGER Are no bacterial substances at any level influential in producing it?

DOCTOR KOELLE In the concentrations in which they are produced in the bowel I doubt it very much but one cannot be over-dogmatic because I know of no specific evidence either for or against

DOCTOR CODE In extension of that point Doctor Ingelfinger while the concentration under certain disease states might remain the same the ability of the materials to be absorbed might be very greatly altered One of the things we know practically all about (there is a host of them in gastrointestinal physiology) is change of rates of absorption that occurs with alteration of mucous membranes

CHAIRMAN ALMY While we are on the subject I thought you would all be interested to hear of some findings which Doctor H A Gordon has had with germ free animals at Notre Dame University

DOCTOR H A GORDON There is at Notre Dame a group of seven investigators including myself who are interested in the effects of the presence of bacteria that are most common in life compared with their absence Among these investigators are Renner Weeks Trier Irving and a few others I am just a link in this chain

Our rats are classified as germ free *Lactobacillus* contaminated and normal conventional animal By germ free we mean an animal which was born and

QUESTION. In my experience, using the balloon technique, when we have the balloon either in the stomach or colon we notice that when we first start we have a certain amount of pressure in the balloon either water or air, which stimulates a certain amount of activity and subsides while the stomach and colon adjust themselves to certain amounts of pressure. For each subject, however there is an optimum pressure which keeps motility going. With the varying degrees of pressure we cannot confirm that the colon is inactive most of the time. I am wondering if Doctor Code uses a fixed pressure in all the patients and has not reached the point where there is a sufficient amount of stimulation to give activity continually. Each subject adjusts himself to the amount of the pressure in the balloon. There is always activity of the colon and the stomach.

DOCTOR CODE. I think the answer is contained in what Doctor Quigley has pointed out and which we have confirmed that if one pressurizes the balloon system it will stimulate activity. The pressure that we have attempted to use is less than 15 cm. of water. In filling the balloons or in letting water trickle into them a little reservoir is always held at 15 cm. above where we think the balloon is and then we allow some minutes for that to trickle in. We try to fool the bowel just as they used to fool the thyroid. We try to sneak water into the balloon without disturbing the bowel and simultaneous records are taken with the pressure pickup with the balloon filled or empty without altering the pattern in the pickup unit. The latter is so small because it is specifically designed for testing the motility that it would not alter our experiments. For other reasons than the balloon experiment I agree that a level can be found at which the activity would be more or less continuous. It gives entirely different data from the types of tests mentioned by the inquirer.

CHAIRMAN ALMY. Doctor Kern does that explain the continuous activities in your tracings showing difference in pressure?

DOCTOR KERN. I do not believe so. We have studied sigmoid motility at various pressures ranging the pressure in the balloon from 3 to 4 cm. of water to 20 to 25 cm. of water and there was absolutely no difference in the tracings. At the higher levels of pressure the base line of the tracing would subside over a period of 15 to 30 minutes to 6 or 8 cm. of water pressure and from then on the tracing would have exactly the same pattern that it had had at lower levels.

DOCTOR GRACE. Using the same level of pressure in the gut water recording apparatus and by various techniques for maneuvering the mood and feeling state of the patient it can be seen that both increase in motility can take place and decrease and total cessation of motility occur under some circumstances. I do not think it can be said that the balloon itself is invariably associated with motility functions of the gut.

DOCTOR SLEISINGER. Doctor Koelle do you have any evidence on the relationship between function in the ileum or colon in animals and human beings isolated or *in vivo* and on the levels of specific and nonspecific cholinesterase in the gut?

DOCTOR KOELLE. Some studies that we have done on megacolon which will be published shortly in *Gastroenterology* show differences in specific and nonspecific cholinesterase in the spastic and hypertrophied portion. That was

that there are other causes which probably affect the size of the cecum in this interpretation There are at least two variables One is the diet or the dietetic history and the other is the bacteriological status If one of them acts alone the discrepancy is not as spectacular as it is if both act together

There is one more item I should like to mention If you take several animals from a whole group of germ free animals and contaminate them with a bacterium then these latter animals compared with the ones which stay germ free will reduce their ceca very rapidly within a matter of weeks The invasion of bacteria seems to affect the size of the cecum considerably Another very important point is with regard to the bacteria used to contaminate the animals If we contaminate the animals with *Lactobacilli* we find a reduction in the size of the cecum If we use *Staphylococci* for instance then the cecum will stay as large as it was originally These are accidental observations and were not made as systematic work The point I wish to make however is that when we talk about a bacterial effect we do not like to generalize and say the bacteria but believe we have to say specifically what bacteria

DOCTOR INGELFINGER Was there any gas in the ceca?

DOCTOR GORDON There was gas present chiefly at or before weaning time Baby rats cannot burp apparently and therefore in the first generation of hand fed animals we regularly find gas in the cecum In the other categories we do not find it

DOCTOR INGELFINGER The germ free type category?

DOCTOR GORDON We do find it there up to weaning when hand fed We think there is a certain degree of airophagia with the methods we use

DOCTOR M L TAINTER (*Sterling Winthrop Research Institute Rensselaer N Y*) I find I am confused as a result of some of the presentations Doctor Code and several of the others I think emphasized the fact that the peristaltic waves they perceived are nonprogressive nonperistaltic whereas Doctor Quigley showed very beautifully that they were definitely progressive Is this due to the technique of measurements type of experimental animal material studied or did I misunderstand the various speakers?

DOCTOR QUIGLEY There certainly is a progressive type of activity which moves from one portion of the colon to the other It can move upstream or down It does not occur very frequently and the evidence that we have available indicates that under normal conditions it probably occurs only a few times a day It is quite possible to make an investigation for a long period of time and see no indication of this type of motility

DOCTOR CODE Doctor Tainter in those old observations of Templeton and Harrison which Doctor Quigley indicated with the sliding waves coming down the activity was a whole complex There were type II and type III waves superimposed on this complex and they showed that that was transmitted It was this sort of pattern rather irregular he traced through the bowel That is not a peristaltic wave it is made up of haustrals and tone changes and is a propulsive mass movement The only question I raise about it is that if you have two segments of bowel with balloons or pressure recorders in them do they occur so that the head one the proximal occurs first and then the distal one or with proper recordings are they simultaneous? The description

raised in a sterile environment and fed sterilized diets All bacteriological criteria show that living contaminants in this animal are negative This is our prerequisite "*Lactobacillus* contaminated' is essentially the same except that, at birth, the germ free animal has been contaminated with a human strain of *Lactobacillus* from the mouth which spreads in this bacteriological vacuum, as we like to call it and where it will stay indefinitely Our normal conventional' animal is the normal animal

We generally like to work by generations as follows the first generation is a cesarean born animal from a conventional mother The operation is performed under sterile conditions and the babies picked up and reared in germ free units, as we call them However owing to the fact that we cannot collect sufficient normal rat s milk, we feed them on artificial sterilized formulae The formulae are not comparable to the normal rat's milk and compared with the normal animal we never get as good growth as we do with the normal mother s feeding

The first generation, therefore, is cesarean born from a normal conventional mother and hand fed on artificial formulae for two to six weeks The second generation is born from germ free dams and fed on mother's milk We regard this difference as very important The first generation, we think will show the combined effect of an abnormal dietetic history prior to weaning and an abnormal bacteriological status It is this phase of life which is chiefly affected The later two groups will be free from the abnormal dietetic history and will show the effects of the abnormal bacteriological status only

The results that I should like to present to you originate from rats of mixed sexes, weighing from 150 to 200 grams Both the germ free and the *Lactobacillus* contaminated groups were composed of healthy rats From the clinical standpoint, they offer all criteria of health that is, they have a normal weight and growth curve and in addition reach their sexual maturity at the same time as the conventional animals Some of these rats have a relatively huge cecum so that when we establish the growth curve of the animal we have to deduct the weight of the cecal contents

When I speak of the relative size of the cecum I must apologize for not having the exact data with me These are relative figures which really represent minimum differences If I could substantiate these conditions with absolute data the differences would be even greater We perform a comparison of the size of the cecum which is really the weight of the cecum wall plus the cecum contents per hundred grams weight of the animal

The results are quite clear cut The germ free animal compared with the conventional animal has a tremendous enlarged cecum It is tenfold sometimes twentyfold or even more However in the first generation only we have the combined effect which we mentioned in regard to the *Lactobacillus* contaminated animal Then it seems the presence of bacteria reduces the size of the cecum or cecum contents If we take a germ free animal through successive generations, then we shall find a smaller cecum than in the first generation It will never reach the size of the normal cecum

Finally in the *Lactobacillus* contamined cecum we have a value between the normal conventional animal and the germ free one It seems to us therefore

Part II Etiology of Colonic Disorders

CHILDHOOD EXPERIENCE AND COLONIC DISORDER*

By Dane G Prugh

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Introduction In recent years signal advances have been made in the under standing of the psychophysiologic aspects of colonic function [8, 85] The determinants of disturbances in function of this organ however have remained somewhat more obscure Although immediately precipitating factors or trigger mechanisms of an emotional nature have been convincingly demon strated[19, 35, 63, 70] for a variety of symptomatic pictures the etiologic basis for the involvement of the colon as the particular representative of the participating organ system is still unclear In an attempt to come to grips with this and similar problems dynamic psychiatry paralleling the approach of embryology has postulated from clinical observations a genetic etiological framework within which the experiences of the early years of life are felt to influence later psychophysiologic function limited only by the genic [17] potentialities and biological equipment of the organism The direct study of childhood experi ence thus has pertinence for an inquiry into the causality of colonic disorder The present investigation was designed to explore within the range of current knowledge the degree of influence as well as the nature of operation of certain variables in childhood experience as they bear individually or in combination upon later functioning of the colon

Review of the literature Through the centuries beginning with Aristotle child rearing practices have received much attention from philosophers and educators More recently discussion of such practices has been pre-empted by child psychiatrists psychologists pediatricians anthropologists and other professional personnel [4, 7, 9, 0, 35, 46, 71, 76] accompanied by violent agitations from time to time in the movement of the pendulum of opinion During the past fifty years increasing weight has been given to the effect of environmental influences in infancy and early childhood upon later patterns of behavior and psychophysiologic function Freud s studies underlining the genetic or his torical factors in personality development gave the main impetus to this growing emphasis His observations regarding the interrelation between personality structure and colonic function [6] led to seminal hypotheses which have influenced most later studies of this subject Among such hypotheses was that relating to the effect of toilet training practices upon later defecation patterns and upon the physiologic functioning of the various structures in volved in the act of elimination

Various attempts have been made to test Freud s hypothesis which was based on the retrospective data available from the analysis of adults and was put forward during a historical epoch in which early and rigid methods of toilet

Th t dy w m d po bl th gh b q t f om th t te f th l te Ha ld E B t

by the radiologist is that it all occurs in two or three seconds Our records all show that with accurate recorders they are simultaneous It is a whole segment and not a true peristaltic ring that moves in the esophagus or in the small bowel We just have not seen any peristaltic movement that we could distinguish in the large bowel The rings that are there are haustra They stay put and don t migrate The original literature suggested that the mass movement was a peristaltic ring that goes 'swish ' Then the pressure should rise right behind it It does not do that The pressure stays up and relaxes slowly If it is a peristaltic movement it takes a minute I don t think that it is a peristaltic movement I am going to suggest that for practical purposes the most difficult thing for me to get around is Doctor Almy's and Doctor Kern's recording where they did show progression It may be by balloon it may be dissipation of pressure it may be the pickup methods by transducer It it occurs simultaneously I think we shall have our backs to the wall It cannot be a peristaltic ring moving down

DOCTOR QUIGLEY I do not look upon peristalsis in the manner that Doctor Code did that is on the ring going down But as described in most individuals a mass movement with an entire section contracting with a number of com ponent contractions involved in it This is a mass contraction rather than a traveling ring It is different from the peristalsis which occurs in the small intestine being more of a mass type and it will hold for longer periods of time

over specificity of influence by this particular variable by pointing out that cross cultural surveys reveal no one to-one relationship between any single child rearing practice and specific symptomatic pictures or personality development.[7, 16, 18, 60] Such psychiatrists as Fries[27] and Pearson[61] apparently feel that generalization is impossible regarding the effects of bowel training particularly in regard to personality development

Although it may be possible that no broad conclusions are tenable concerning the effect of bowel training when considered out of context certain recent studies indicate that perhaps different constellations of child rearing practices may produce varying effects upon some aspects of adult psychophysiologic function Sociologists and anthropologists appear to agree that our North American society—and indeed Western society in general—places earlier and more rigid emphasis upon training for cleanliness with parallel emphasis upon other child rearing practices such as weaning than do primitive or isolated societies[7, 19] Furthermore middle-class morality appears to weight the early achievement of control of bodily functions more heavily than is the case in most lower socio-economic groups[18, 39, 76] There is evidence as well that bowel training and other techniques accompanied by greater demands upon the child for early control became much more rigid in middle-class segments of Western society during the rise of scientific pediatrics in the context of complex social changes which both precipitated and accompanied the development of bowel training following the turn of the century[9, 20, 1, 76] In relation to these changes Halliday[35] has produced statistical material which indicates that in Great Britain at least an increase in the incidence of gastrointestinal and other disorders of psychophysiologic function has come about in the generation first exposed to these more scientifically impersonal and demanding techniques of child rearing Evidence of this nature however suggestive is difficult to evaluate Unfortunately a knowledge of the comparative incidence of colonic disorders in different social class groups or in different societies is not available at present

As can be readily seen methodological problems arise in the course of consideration of the aforementioned set of interrelationships Most of the studies mentioned have been retrospective in character without available control cases and have involved small numbers of patients The few longitudinal studies upon which reports have been published leave great gaps in the necessary data mainly because of the theoretical framework or methodological approach employed at the outset of investigation[1, 25, 30, 33, 55, 65] Problems involved in diagnostic assessment of the etiology of colonic disorders have understandably contributed to confusion The problem of definition of criteria for coercive training has not been solved completely Certainly marked variations have existed even in the interpretation of prevalent criteria formulated principally by Huschka[1] The complexities inherent in the study of human behavior are reinforced by the technical difficulties involved for example in assessing the unconscious psychic influence of the mother upon the child during bowel training procedures an influence which may be in direct opposition to the mother s observable behavior Lastly tremendous pitfalls are produced by the attempt to isolate one or two variables from the broad

training were predominantly employed Examples of currently adverse reactions, behaviorally and gastrointestinally on the part of children undergoing severely punitive or early bowel training procedures have been recorded many times [5,3,42,5,64,72] Such investigators have documented instances of the development of constipation, soiling, and diarrhea as immediate colonic responses to coercive bowel training and to repeated local manipulation of the ano rectal region with suppositories or enemas by over zealous mothers The reversibility of such symptomatology in small children by means of psychotherapeutic measures designed to mitigate coercive training practices employed by their parents has lent further support to the inference that bowel training methods were important etiologic factors in the development of colonic disturbance [18,52,64] This inference has been supported by detailed material drawn from the psychoanalysis of older children[5,19,3,41] and adults [1,25] exhibiting constipation diarrhea or other colonic symptomatology with definitive emotional components Data is also available regarding the high incidence of coercive training practices employed by parents of older children with soiling [5,32,42,51,67] ulcerative colitis [63,69] and the nonaganglionic type of megacolon [32]

Most of the studies cited have been carried out on relatively small groups of patients In an investigation of a much larger group of children referred for psychiatric problems Huschka[41] produced some evidence of the relationship between coervice training and bowel dysfunction (principally constipation) in a small proportion of the total number These cases were studied retrospectively and no controls were employed Unfavorable psychic and behavioral respon es were far more frequent than were colonic distorders In the only pertinent published material deriving from an on going longitudinal study Roberts and Schoelkopf[65] found an incidence of constipation of approximately 20 per cent in a group of over 700 well children of preschool age These children were studied in a clinical setting where more permissive methods of bowel training were encouraged In most of the instances where constipation was apparent however the mothers continuing preoccupation with bowel and anal function appeared to be a strongly causative factor with local manipulation of the anorectal region being employed in over one fourth of the reported cases

The use of statistical methods of study in clinical research of the type already summarized has been difficult for various reasons consequently such methods have been rarely employed in the area of bowel training In a parallel study of the relationship between coercive bladder training and the development of nocturnal enuresis however Bostwick and Shackleton[8] were able to demonstrate a statistically significant relationship between these two variables thus corroborating the impressions of Despert[14] and others

From the foregoing it is apparent that a suggestive correlation between bowel training and colonic dysfunction has been demonstrated by a number of investigators employing different frames of clinical and theoretical reference Unfortunately for the cause of simplicity however other instances involving an absence of colonic symptomatology have been recorded on the part of children undergoing at least superficially similar bowel training practices [4,41,60,66] Also cultural anthropologists have recently contributed to the controversy

through adolescence From this group 42 case records were drawn These represented the cases in which data were available regarding the time of completion of training (in most instances the date of onset of training as well) Unfortunately few significant facts were apparent from these histories regarding the degree of coerciveness associated with the act of training or the emotional climate in which such training took place In instances where disturbance in colonic function was noted careful physical examination at the time of occurrence of symptomatology had revealed no pertinent causes of predominantly somatic origin Virtually all the children included here were of at least average intellectual capacity On the basis of timing of training alone the trends shown in FIGURE 1 were found It may be seen that the incidence of colonic dysfunction was virtually twice as great in the group of children with early training as in the group with average training Values of χ would indicate however that this relationship has relatively limited statistical significance (p = 16) It is to be recognized that a larger case sampling as well as more detailed information might well render this finding of greater or lesser importance When bowel training and colonic dysfunction were assessed in those children completely trained before one year of age for example no strongly positive correlation was apparent between the two variables

Sex distribution among the children showing bowel dysfunction was as follows when considered in relation to timing of training

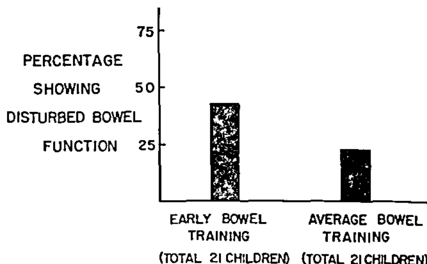


FIGURE 1

context within which they operate in their influence upon the child Such an attempt with respect to bowel training and colonic disturbance for example largely leaves aside the obviou ly interrelated factor of personality development[8, 21, 5, 3] producing an artificial distinction which is unsafe methodologically and unsound psychodynamically It can be safely said that no consistent body of data has appeared to date which elucidates clearly the relationship between childhood experience and later colonic dysfunction

Methods of Investigation Although the methodological limitations just discussed appeared to be formidable ones it was felt necessary to undertake at least a more focused and organized approach to the testing of the hypothesis set forth by Freud in regard to toilet training For this purpose material was sought which would remedy some though clearly not all, of the deficiencies apparent in the literature Accordingly data were obtained regarding bowel training practices and colonic function which were available from a longitudinal study of approximately 100 children begun more than 19 years ago * In addition to this material gathered during the precess of training from a normal population similar data were collected retrospectively from a patient population' of 45 children all of whom exhibited various degrees of colonic dysfunction in which an emotional component of significant degree was patently operative For the purposes of investigation no attempt was made to correlate the nature or severity of bowel training with specific characteristics of later personality development

In the definition of coercive training the criteria formulated by Huschka[41] were employed This investigator used the term to denote premature institution of a toilet training regime and overactive destructive training method Training begun before the age of eight months or completed before the age of eighteen months was considered by her to be coercive in character as was training embodying such direct methods as persistent punishment and the use of strong restraint on the toilet as well as more indirect techniques of shaming the child or placing a high love premium on toilet performance

Because of the nature of the data available in this study Huschka s criteria were broken down into two main categories covering timing and nature of bowel training A natural subdivision of her criteria would appear to lend itself to this usage Early training thus refers to that begun before eight months or completed before eighteen months of age Average training includes that begun later and completed later with an arbitrary upper age limit of three years Training which was coercive in nature was considered to be that fulfilling Huscka s criteria regarding methods employed In most instances where data on both facets of bowel training were available a high correlation between timing and nature in terms of coerciveness as defined by Huschka was present

Results

A *Data on group of well children (normal population)* Records on approximately 90 children studied longitudinally were available from infancy

Th m t l w s g th red by Doct Le J k f m th d f th G wth St dy C d t by Docto H ld Stuart Prof r f M t rn l d Child H lth H d b f f bl H l h Bost Mass

B *Data on children with established colonic disorder (patient population')* Because of the limited material available in the well child group regarding the 'nature of bowel training it was decided to study a group of children on whom pertinent and psychiatrically sound data were readily at hand For this purpose 45 children were selected all exhibiting some form of disturbance of colonic function of persistent degree These children had been referred for psychiatric study from the medical service of a children s hospital In all instances careful methods of psychiatric diagnosis indicated the presence of strong emotional components in the symptomatology Current causes of predominantly physical origin had previously been thoroughly eliminated Relevant facts about this group follow

1 Diagnostic category

C t g ry	Number
Constipation	7
Incontinence	10
Diarrhea	4
Spastic colitis	2
Ulcerative colitis	22
Total	45

2 Age range

Ag	Numb r
3–5	7
8–10	35
11–17	3
Total	45

3 Sex distribution

D gnosi	M le	Fem l
Ulcerative colit s	12	10
Others	18	5
Total	30	15

Figure 2 indicates the type of toilet training experienced by the 45 children studied In all cases labeled openly coercive training was both begun before eight months *and* completed before 18 months of age in addition to being strongly punitive in character Fortunately data on this variable were quite complete The category labeled overly permissive refers to those children for whom the parents took no overt responsibility in training In virtually all of these cases however the parents had strongly unconscious needs for rigid conformance and utter cleanliness on the part of the child In such cases the parents appeared to show reaction formations against such obses sive compulsive needs exhibiting superficially permissive and overindulgent

	Early	Average	Total
Boys (21)	28.0%	16.0%	44.0%
Girls (21)	11.8%	5.9%	17.7%

In these small groups, then, boys showed the higher incidence of disturbance in function under all circumstances.

Of the 9 children (21.4 per cent of the total group of 42) who showed disturbance in colonic function associated with "early training" the following distribution occurred:

Constipation	6
Fecal incontinence	3
Total	9

Because of limited information the length of persistence of symptoms in these children cannot be tabulated with accuracy. The following table indicates the data available regarding the *last* date of reporting of symptoms by the mother or responsible parent.

Age	Number of Children
2–3 years	4
3–4 years	1
5–6 years	1
7–8 years	1
8–9 years	2
Total	9

Therefore, 19.1 per cent of the group of 21 children undergoing "early" training exhibited symptoms of colonic dysfunction continuing beyond the age of five years.

For the whole group of children information is available regarding the time of achievement of bowel control. For purposes of later comparison with data on children studied recently by Roberts and Schoelkopf this material is included.

Age of achievement of bowel control	Percentage of children (42)
Before 8 months	10.0%
8–12 months	30.0%
12–18 months	32.5%
18–30 months	27.5%
Total	100.0%

By 18 months, therefore, 72.5 per cent of the children had achieved control; by 30 months of age 100 per cent had performed similarly.

summarized in the following table which includes various types of physical disease localized to the colon and occurring during the period of training

Type of involvement	
Local manipulation	48 9%
Local disease (infectious diarrhea etc)	11 1%
Total	60 0%

In an attempt to assess the patterns of autonomic response to stress in the families of the children studied the following data were obtained in relation to the presence of disturbances in lower gastrointestinal function in the patients close relatives Such disturbances appeared retrospectively to bear a strong emotional component and included such symptoms as diarrhea constipation soiling (in childhood) and other manifestations without apparent physical disorder Data were available on only 25 of the 45 children

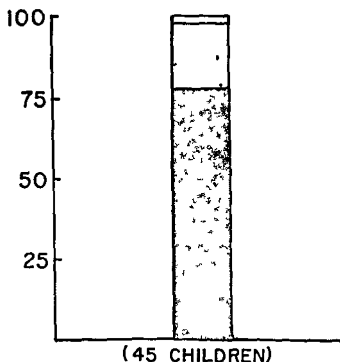
Childhood Experience and Colonic Disorder

Family [illegible]	Number
Mother and father	2
Father alone	7
Mother alone	6
Paternal grandparents	1
Maternal grandparents	2
Total	18 (72%)

Thus in 18 of 25 cases (72 per cent) some evidence of familial tendencies toward the development of gastrointestinal response to emotional stress was suggestively present

C *Individual case material* The foregoing data deal with possible correlations of a statistical or quantitative nature between coercive bowel training and later colonic disorder Certain additional material of a qualitative character however bears more directly upon the possible implication for individual children in particular contexts of such early experience in later dysfunction As mentioned earlier reports of cases analyzed or treated psychotherapeutically provide abundant material of this kind Several cases among a number in the writer s experience are cited briefly (1) John a seven year-old boy with acute fulminating ulcerative colitis was treated psychotherapeutically for one and a half years in conjunction with appropriate medical regimes Resolution of symptomatology occurred within one week following the initiation of psychotherapy and freedom from exacerbation has persisted for three years to date As indicated in an earlier report a definite emotional component was implicated in the precipitation and perpetuation of his symptoms[63] The following chart illustrates the characteristically pathogenic quality of thoughts or fantasies related to messiness or dirtiness (and in later interviews bowel function in general) He had been coercively trained with the repeated use of suppositories and enemas beginning at three months of age with apparent establishment and persistence of bowel control until the onset of

DISORDER AND BOWEL TRAINING



OPENLY COERCIVE BOWEL TRAINING

OVERLY PERMISSIVE TRAINING

FIGURE 2

handling of their children although the underlying feelings appeared to be perceived by the children

In the children listed early weaning was a common feature Although the data are not complete severe colic in the first three or more months of life was present in over half of the cases Frequently soiling when present was associated with wetting and training for bladder control in most instances had also been coercive in character Virtually all the children were of at least average intellectual capacity

An interesting finding was that nearly one half of the 45 children were known to have experienced repeated and strenous local manipulation of the anorectal region by means of the parents usage of suppositories enemas and lubricants during the course of bowel training (others may have undergone similar experience since a number of parents were quite defensive and forgetful in discussing this point) The data concerning local involvement of this region are

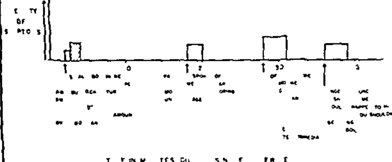


Figure 3

Discussion

A *Criteria employed* A discussion of Huschka's criteria[41] regarding coercive bowel training necessarily entails some treatment of the known facts of growth and development Huschka assumed that aside from the punitive character of the coercive training approach efforts to force the child to achieve voluntary bowel control which are *begun* before the age of eight months ordinarily place demands upon the child for which he is not ready developmentally This assumption was based upon the observation that local con

symptoms at six and one half years of age His mother was a strongly controlling woman with intense needs for utter cleanliness and orderliness and with much ambivalence toward this boy her only child As can be seen in FIGURE 3, the sight of a diaper filled with stool produced hypermotile colonic action in this psychologically and physically predisposed boy (similar situations produced equivalent results in a number of other instances involving this boy)

(2) Jane an eight year old girl with mucous colitis characteristically experienced abdominal pain followed by diarrhea whenever she would pass the door of the family bathroom at a time when it was occupied by her younger brother who locked the door and enjoyed keeping Jane out For six months these symptoms occurred at no other time Early in psychiatric treatment, Jane verbalized her fear that she would not reach the toilet in time when her brother shut the door against her Later, however she expressed her previously unconscious wish to cover the brother with feces, as an expression of resentment toward her mother Jane had been coercively and completely bowel trained by seven months of age She repeatedly described her sensation of contraction in the anal region (without diarrhea) whenever she saw a toilet saying ' It gets tight back there ' Jane s mother, a tense anxious woman had been strongly driven by her current fear of her own mother s critici m as well as by deeper psychic needs of a compulsive nature to "keep Jane absolutely and spotlessly clean

Many more examples could be cited Additional evidence however, comes from cases of constipation and oiling in small children Paralleling the experience of other investigators cited earlier the writer has had experience in working with the mothers of 12 such children In all instances relatively prompt reversal of symptomatology was possible with the use of a supportive psychotherapeutic approach dealing largely with the mothers attitudes toward bowel function resulting in a de-emphasis of such attitudes and a diminution of rigidity or punitiveness in this area One such case is cited

Bobby a three year old boy had suffered from constipation of severe degree from early infancy No predominantly physical source of his symptoms could be seen and careful history revealed that the mother had been concerned about constipation since Bobby s birth She had felt the need to give him a suppository or enema if he went more than 12 hours without a stool urging him frequently to move his bowel and spending hours examining his stools and their consistency Four interviews by a pediatrician sufficed to help this woman gain superficial relief from the guilty fear that Bobby would swell up like a pregnant woman' if his bowels were not empty Repeatedly the mother stated that if this happened It would be my fault since Bobby might die as her first child did *(from intussusception)* before I knew what was wrong Through supportive contacts with the physician the mother gradually became able to give up local manipulation of the anorectal region and to allow Bobby greater independence in taking over his own handling of toilet procedures Following the initiation of such an approach the constipation completely disappeared within four weeks Follow up for two years revealed no return of this particular symptom

until at least the latter part of the first year Later during the middle of the second year certain rebellious and aggressive impulses (the so-called stage of normal negativism) come into ascendance in relation to the child s developing independence and his struggle for mastery over his mother as well as his own impulses The psychological hiatus thus created at the end of the first year may account for Fries s observations that training begun (though not in a punitive fashion) at the end of the first year seemed in general to proceed more smoothly than that begun at 15 months of age

Moving from neurophysiological and psychological considerations one can readily see from a perusal of appropriate studies that the ages at which children actually achieve bowel control can be influenced by variations in toilet training practices[46, 48, 60] Even though the sample is relatively small the ages of achievement of control by the children in the present study may be pertinent in this connection when contrasted with the results of another study undertaken at a different time and in the face of differences in child rearing practices In the group of well children studied by Stuart data were gathered approximately seventeen years ago and the majority (72 5 per cent) achieved control by 18 months of age with 40 per cent achieving control by one year In the following table the data from Stuart s study appear to reflect the earlier and more rigid bowel training practices of the day dictated by scientific pediatrics and social sanction in contrast to the more permissive practices carried out approximately 15 years later and reflected in the findings of Roberts and Schoelkopf

	Percentage of Children Achieving Bowel Control by 30 Months
Stuart s study (*ca* 1935)	100 0%
Roberts and Schoelkopf s study (*ca* 1950)	88 1%

As might be expected the use of studies such as these as normative standards or even as material for comparison is made even more difficult by the undoubted differences in ethnic background social class structure *etc* between the two groups For example Kardiner[48] has assembled data on one small midwestern town with a population exhibiting ethnic characteristics undoubtedly different in character from either of the above groups (from predominantly urban areas) which indicates that the inhabitants there require complete control from their children by 15 months to two years of age Lewis study[63] of contrasting patterns of child rearing in rural and urban populations supports the inference that the age of achievement of bowel control by children in the two settings may be quite different even in the same era of ideological approach to training practices Allowing for variations in cultural patterns and historical development however it would appear that during the past thirty years in which records have been available the majority of children in this country have achieved control of bowel function at least by the age of two and a half years[33, 65]

From the foregoing considerations it is apparent that although no absolute criteria can be established for the onset and completion of training certain lower limits can be set which appear to rest securely upon a foundation of known neurophysiological and psychological facts More exact knowledge is of

ditioning of the rectal sphincter by reflex action alone appears possible at this time.[33] Conditioning with the use of suppositories has been shown to take place as early as six weeks of age.[77] Huschka's stipulation that training *completed* before eighteen months of age is similarly out of line with developmental abilities and is therefore coercive was based upon the recognition of the fact that myelinization of the pyramidal tract presumably necessary for effective voluntary control is not completed until the twelfth to eighteenth month of life.[23] Although these facts have been definitively established in broad outline, it is true that individual developmental variations in readiness for voluntary control do occur as Huschka recognized. The studies of Langworthy[50] and others[48] raise the additional possibility that function may be necessary for or at least may promote the development of myelinization. Some controversy accordingly exists in regard to the establishment of the age of readiness for voluntary control.

Although the neurological aspects of this problem are not completely understood, certain phenomenological observations are pertinent as are basic facts regarding psychological development of the infant. It has been noted in the present study that a significant number of children (40 per cent) achieved apparently lasting control by the age of one year, a smaller proportion (10 per cent) performing similarly by the age of eight months. Nevertheless observations by Isaacs,[4] Huschka[41] and others would support the conclusion that breakdown of control achieved at this early age is more frequent than that achieved by 18 months or later. (The numbers in the present series are too small to cast significant light on this matter. Suffice to say that no such trend could be seen.) Fries's studies[7, 8] indicate that training begun prior to six months takes longer for completion than does training begun at the end of the first year. Although voluntary control is accordingly possible for infants under one year of age, one is probably justified in concluding as Huschka does that such control occurs at the cost of some neurophysiological strain and emotional tension. These manifestations would appear to arise during the transition from reflex conditioning of the external anal sphincter to the more complex stage of voluntary control involving associated and reciprocal activity of the lower colon and internal anal sphincter, as well as direct participation of the various accessory muscles of elimination.

In addition to such components as neuromuscular readiness, the ability to sit alone, some capacity for at least nonverbal communication to the mother of the need for defecation, and a certain predictability of bowel movements, voluntary control appears to involve as well a psychological readiness on the part of the child for control of the impulses to soil or to withhold the stool, activities which appear to provide a certain type of primitive pleasure for the infant and small child.[4] Such a desire to control these primitive impulses is definitely dependent upon the degree of security in and satisfaction from the relationship with the mother or mother substitute (a fact supported by parallel experiments with dogs[64]). Differentiation of the infant's personality to the point of development of the capacity for communication and for the entertainment of a desire to please the mother by depositing the stool appropriately rather than according to pleasurable impulse does not appear to be consolidated

in a broad sense to support the conclusion that it is worth while to encourage training practices which are not coercive, by the definition employed in order to prevent possible disturbance in colonic function and to foster most ideally the development of the complicated interrelated patterns of somatic and psychic functioning involved in healthy eliminative processes In this connection the results of a controlled investigation by Cooper[12] are pertinent This investigation studied the reactions of two groups of approximately 100 children each a preventive program of child guidance being offered to the parents of the one group including a more flexible and chronologically later approach to bowel training Her impression was that the incidence of bowel training problems possibly conducive to later colonic disorder was reduced by such an approach in contrast to the group to whom no such guidance was available

C. *Sex incidence* It is of interest that in both groups boys showed a higher incidence of disturbance than girls (nearly two and a half times more such disturbances in the well child group and twice as many in the patient group) This finding of limited significance in these relatively small groups is given greater importance by the impressions of analysts such as Benedek[8] and in particular by the study of 779 well children carried out by Roberts and Schoelkopf[65] In this large group it was found that there was an incidence of 16 1 per cent of bowel training problems (resistance soiling *etc*) for boys against 8 1 per cent for girls In this study however girls showed a higher incidence of constipation than did boys This was true in the present study with soiling appearing principally in boys Small samplings make this finding inconclusive however except in so far as support is given to the conclusions of Roberts and Schoelkopf

A finding of this nature lends itself to at least two interpretations One possibility is that boys are to a greater extent than girls constitutionally predisposed to the development of colonic disorders or being more aggressive after infancy[65] are more firmly predisposed to resist toilet training procedures The other available interpretation is that mothers in North American society experience greater conflict in handling the bowel training of boys In all likelihood both factors are operative It is easier to test the second hypothesis however and available material from this and other studies would tend to confirm the greater intensity of conflicting feelings on the part of mothers dealing with male children related to their own feelings of rivalry with men and other deeper psychic sources Ulcerative colitis however does not seem to show a decided sex incidence[63] This finding is unexplained

D *Personality of parent* It is obvious from the case reports cited earlier brief as they are that the mothers of these children with continued colonic dysfunction exhibited personality disorders predominantly of an obsessive compulsive nature Most of the reports in the literature have described similar personality structures of the mothers of such children[6, 8] From careful studies it would appear that mothers with strongly compulsive personalities often gain unconscious satisfaction through their preoccupation with their children s bowel functions a satisfaction related to their need to hold in check by such rigid defenses their own rebellious desires from childhood to be independent and pleasurably messy (Other psychic needs usually unconscious are of

course, to be sought on this subject In its absence, however, Huschka's criteria appeared to be workable and appropriate for use in this study

B *Apparent trends regarding the effect of coercive bowel training* From the foregoing data, certain broad trends emerge A perusal of the material derived from the study of children with continuing and severe colonic dysfunction ('patient population) would indicate that in these patients a high correlation exists between coercive training, as defined by Huschka and later colonic disorder It is true that data bearing on the timing and character of bowel training as well as earlier bowel function were largely retrospectively derived, following referral of these children for psychiatric study at the ages listed In 18 out of 45 cases however data were available which were accumulated through medical study and follow up from early infancy, indicating that retrospective histories of coercive training methods and anorectal manipulation were accurate In 10 additional cases principally those exhibiting soiling no interval of freedom from symptoms had been present following the training period In these cases, as in others, the parent s current attitudes toward bowel training matched closely with those recorded retrospectively by several independent observers

From the normal population less significant conclusions can be made It seems apparent that coercive bowel training played a role in certain instances of colonic dysfunction Nevertheless statistical validity cannot be attached to an exact correlation between the two variables The fact that such disturbances in bowel function as are recorded were not recognized to have persisted beyond the ninth year of life raises several questions For example, the limitation of exact data renders follow up material sketchy and inexact It is possible that with the growing independence of bowel control which develops in the child following preschool years milder degrees of dysfunction might not have been reported From the histories of patients exhibiting various types of colitis or other colonic disorder which develop during adult life it is apparent that frequently an interval of relative freedom from symptoms occurs during later childhood Nevertheless the present study does not justify the conclusion that early, and (according to Huschka) thereby coercive training is the major factor in the development of later colonic dysfunction in the absence of associated personality disorder (The current investigation makes no attempt to bring into focus the relationship between coercive training and personality disorder without associated colonic disturbance although there is considerable indication that personality disorder of an obsessive compulsive type may be associated with such childhood experience as at least one factor)

From the material at hand then it can be said that in children and adolescents with definite and continuing colonic disorder coercive bowel training appears to have been a significant factor in the etiology of the disturbance No exact correlation could be made between the character or timing of training or local manipulation of the anorectal region and the type of bowel disturbance It does not follow from the available data that coercive training necessarily produces colonic disorder even though there is some evidence that such will be the case

The material from this study and from others reviewed earlier would appear

thesis[14] as well as Freud s earlier suggestion [5] that physical illness or local stimulation can serve to render bowel function the focus of a fixation of energy in the minds of child and mother to which the child may later regress in the face of outer stress or inner conflict In the case of children undergoing physical illness or manipulation (enemas etc) the breakdown of control over bowel functions and associated impulses which may occur as the result of the physical stimulus has been known to arouse considerable anxiety over the threat to cleanliness in children with strong needs for conformity and through the resulting tension to intensify the gastrointestinal symptomatology

Data from the present study as well as that of Cobb Jones and White on mucous colitis [11] would seem to suggest that predisposition to autonomic response of the gastrointestinal system to emotional stress may be an inherited potentiality A study by Jorup[43] of infants with colonic hyperperistalsis in comparison with a group of normal controls appears to lend support to this thesis with the finding that the parents and siblings of the patients to a higher degree than the families of the controls exhibited psychosomatic disorders of the gastrointestinal tract Jost and Sontag[44] have adduced evidence for the inheritance of patterns of autonomic response using monozygotic twins and other well children Fries s studies[27] of the difference in activity types among infants from birth on are also pertinent The conclusions of Van der Waals [75] who has summarized the genic work on identical twins by Hartmann and others offer some additional confirmation especially in regard to the probable inheritance of potentialities for certain types of personality traits laid down during the anal period These conclusions are in support of the thesis put forward by Freud [6] and later taken up by Zilboorg [9] in relation to the role of heredity in the predisposition to the choice of a particular organ in the adaptive handling of tensions In assessing the likelihood of operation of such factors in an individual case difficulties may arise from a number of sources For one a type of psychic inheritance of bowel training patterns and attitudes has been seen to exist in compulsive parents through at least three generations [8]

In addition to possible genic influences some suggestive evidence exists for the transmission of hormones across the placental barrier during gestation with resulting effects during states of psychic stress for the mother upon the infant s general reactivity and more particularly as Sontag has indicated [68] upon the activity of the gastrointestinal tract Such infants of such mothers according to Sontag tend to be more active *in utero* and to show greater activity of voluntary musculature and of the gastrointestinal tract with a high incidence of colic and pylorospasm The writer s studies though not statistically significant would tend to support this impression since a large proportion of the children with later bowel dysfunction were known to have shown severe colic in infancy Incidental disease of the fetus might also play a role as could the degree of birth trauma [36] the presence of prematurity the type and duration of the delivery [49] [62] and other factors predisposing the infant to later difficulties in adaptation which might produce the need for the involvement of any organ system in the maintenance of emotional homeostasis The influence of factors of this more general nature as in the case of genic pre

course subserved by such behavior) In most of these instances a very close almost "symbiotic" relationship between mother and child was apparent from early infancy It is clear as Sperling has stated[70] that in children who are affected by severe colonic disorders accompanied by predominant emotional components, the relationship with the mother is at best only a partially satisfying or ambivalent one It is equally clear that the frequently coercive bowel training is a function of the mother's personality structure and therefore only one of a series of restrictive (or in some cases overindulgent) acts impinging on the child's development

From these observations it can be said that the timing and observable nature of bowel training alone cannot be the sole etiologic factor in the development of colonic disorder since mothers with different and warmer relationships with their children can in certain instances adopt the same type of bowel training practice[40, 56, 6] as more rigid meticulous mothers without resulting colonic dysfunction in their children Studies by anthropologists[16, 56, 6] and by child psychiatrists[8, 6] have indicated that it is the motivation and personality needs of the mother rather than her practices alone which determine the meaning of such an experience to a child and therefore his reaction to the procedure Such a conclusion is not in opposition to the findings of the present study indeed the number of children in the normal population who did not develop colonic disorder even in the face of early and presumably vigorous training is sufficient to point the basic importance of the quality of the experience for the child A study of Fries[8] supports this statement In a controlled investigation she attempted to encourage one group of mothers to train their children at six months of age and another group at a later period The mothers in both groups with compulsive personality structures tended to employ early and rigid methods associated with great demands for conformity on the part of the children involved Other mothers regardless of the physician's advice or the time at which training was begun were more moderate in their approach to their children's attainment of control

E *Other etiological factors* Even allowing for the personality structure of the mother as an additional variable in the production of colonic dysfunction it is clear that certain cases in the group of well children described here did not show such disorder Multiple determinants of symptomatology as in other types of organ participation in psychic response are undoubtedly present

For certain types of disorder the data in this study and that of Roberts and Schoelkopf would indicate that the sex of the child either through constitutional differences in activity or through the differential reactions of the mother may be an additional factor

The high incidence of local manipulation and of intercurrent infections or localized disease of the colon in this series and the above mentioned study would support the inference also that such intended or incidental stimulation of the anorectal region operating in a special context and at a developmental point when conflicts over control of bowel functions are most intense may also play a role in the later selection of the colon as the organ for regressive expression of emotional tensions which may arise from a basic disturbance in parent child relationships or other causes This would support Deutsch's

involved The reattainment of voluntary control has been shown to be possible through the use of psychotherapy after the conflicts necessitating the use of the mechanism of regression have been worked through and the patient finds it possible to face consciously the emotions previously long-circuited (Grinker) through the malfunction of the organ regaining a more mature and rationally adaptive approach to the handling of external forces intensifying the inner conflict Involved also is the need for the child (and for certain seriously disturbed deeply regressed adults) to give up the unconscious 'secondary gains which accrue from the adaptive use of the regressively and reflexly functioning organ gains related to the added care given by the parents or relatives or the subtle pleasure obtained from the infantile pattern of excretion

The present communication will not discuss the more complex nature or the relationships between cortical hypothalamic and autonomic functions that are brought into play in such a regressive innervation The current somewhat limited understanding of these processes has been well summarized elsewhere [87] Suffice it to say that there appears to be a release of lower levels from cortical inhibition permitting a return to a point along certain autonomic planes that more closely resembles the infantile state It is possible as Szasz[73] has suggested that the ingestion of food and the action of the gastrocolic reflex may play a role in diarrheal symptoms as opposed to soiling or constipation In such cases situations that reactivate the need for feeding of emotional rather than nutritive supplies in psychically predisposed markedly dependent people (as in many patients affected by ulcerative colitis) may produce reflex emptying of the bowel In such instances however the bowel ordinarily appears to have been conditioned to respond with a change in motility to situations of helplessness that arouse anger relating as in the case cited earlier to conflicts reaching their height during the training period [63]

In the psychophysiologic area a great need exists for more precise data particularly relating to childhood even though the broad outlines sketched here appear to have validity A number of investigations are being carried on currently that may ultimately help to illuminate this well recognized but still dimly understood set of interrelationships

Summary A review of the pertinent literature together with examination of clinical material indicates that few accurate generalizations can be made at this juncture in regard to the exact nature of the relationships between such variables as the specific nature of childhood experience and the pattern of later colonic function within the range of normality Some original data are presented however indicating that there is a relatively high correlation between later colonic disorders accompanied by definitive emotional components and certain types of childhood experience arising in particular contexts Current concepts are evaluated in so far as they bear upon the psychophysiological mechanisms involved in the activation of such disorders and in their derivation from childhood experience The etiology of emotionally precipitated and perpetuated disorders of colonic function and the choice of organ are viewed as possessing multiple determinants These disorders include genetic and somatic in addition to psychic components whose nature and interaction are summarized within the limits of existing knowledge

disposition is difficult to evaluate Much further study remains to be carried out in these areas as actual data are limited

It is thus evident that, although childhood experience in the form of early and coercive bowel training appears to play a role in the production of later colonic disorder, many other variables are undoubtedly implicated The personality structure of the mother (or in rare cases of the father) as the person responsible, in a particular culture at a particular time, for such training would appear *to be the most important of these additional variables* Nevertheless inherited predisposition prenatal experience incidental disease of the colon or local manipulation or sensitization of the anorectal region, sex difference, "activity" (constitutional) type, and other variables appear also to play a role Certainly, more than one variable is necessary, in most instances for the development of later colonic dysfunction

Psychophysiologic aspects A word is indicated regarding the psychophysiologic mechanisms which may produce symptomatology of the colon, in which toilet training and the other variables have played a role Grace[35] and others have well summarized these mechanisms as they apply in adults In children (and at times in adults) the factor of regression to an earlier level of behavior appears to operate generally and selectively [63] Michaels,[67] Szasz [74] Grinker [37] and others have discussed the concept of a 'regressive innervation' which permits the organism in the face of outer stress or inner conflict, to use earlier modes of adaptation in an attempt to preserve the psychophysiological economy or 'emotional homeostasis Such a partial regression apparently involving the autonomic nervous system (parasympathetic branch), may take place to the point of developmentally predominant fixation of energy (toilet training in predisposed children) in the direction of putting into operation a regressive though unhealthy attempt by the organism to solve conflicts in the manner employed when the bowel was undergoing training Such regression can be seen openly in 3 or 4 year old children who begin to soil or to wet the bed during the period of separation from the mother attendant upon hospitalization In such instances the child may verbalize or act out in play concomitantly his hostile feelings associated with emptying the bowel rather than controlling this function in a more maturely adaptive manner [63] A parallel type of regression to a point of fixation determined by frustration or inhibition of function was demonstrated by Wolf in his study of rats [79] which tended to retreat to old infantile patterns (artificially stimulated by the experimental inhibition of vision or hearing during the rats infancy) in the face of a strong current threat to security Animal studies cannot of course be directly transferred to apply to human problems but the parallel significance is clear

In the small child exhibiting regressive soiling ('putting out of the stool at inappropriate times) or constipation (holding in or retaining the stool), conscious voluntary components of such behavior may be present In the older child or adult the conscious symbolically rebellious or other meaning of such symptoms appears to have disappeared and the symptom seems to represent an organ participation in the handling of tensions with the bowel functioning in a 'regressively innervated way involving a return to the level of operation of previously conditioned reflexes in the continued face of the forces

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FUNCTIONAL COLITIS AND CONSTIPATION

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The term 'functional colitis,' is actually a misnomer because first the word colitis from its suffix should mean inflammation of the colon and this condition is not an inflammation, and second the dysfunction implied in the term is usually not limited to the colon but involves the small bowel and sometimes the stomach and even the biliary tract Spastic colitis mucous colitis and irritable colon are likewise inadequate designations Recently, the term enterocolonopathy has been proposed by Bockus but even this more general term fails to indicate the disturbance of stomach and biliary tract which are present often enough to show that the more obvious colonic dysfunction is a part of a general disturbance

This monograph is intended to help correct what has been an absence of interest in the function of the colon and the effect of dysfunction on the general health of the patient In my experience there are three important phases of this subject first the diagnosis must be definitely established with differentiation between this condition and organic disease second the cause must be accurately determined so that treatment may be logically applied and third treatment must be adequate

Diagnosis of functional colitis should be made on the basis of history physical examination X ray and proctoscopy The outstanding symptoms are distress distention and a disturbance in function and constipation in the majority, but diarrhea or alternating constipation and diarrhea in about 20 per cent of cases The distress varies from a mild consciousness of the abdomen to colicky pain is usually shifting in location but may be limited to any quadrant of the abdomen Gas distress and distention may be very severe and are often attended by attempts of the patient to eructate resulting in the habit of belching The history of constipation must be elucidated and most often reveals an initial interference with natural function which later becomes habitual Subsequent to this triad of symptoms (distress distention and constipation) sitophobia and malnutrition easy fatigability and sometimes nausea and vomiting not infrequently ensue Physical examination is important in the fact that it is negative except for in some cases tenderness throughout the colon or in a certain area such as the cecum or sigmoid X ray is all important because first it rules out organic disease of the colon and second it usually shows certain characteristic changes indicative of dysfunction

Hypermotility of the small intestine is revealed by fluoroscopy A three hour film shows a combination of gastric retention of a small amount of barium with rapid progress of the head of the meal through the small intestine and into the colon sometimes as far as the rectum A barium enema without preparation is necessary Preparation with a drastic purgative or enema produces a temporary irritability and must therefore not be used in the first X ray examination which of course may not be satisfactory for the detection of a polyp or very early carcinoma but is an excellent method for determining the presence

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wheat and boiled rice milk toast soft eggs boiled baked or poached warm milk custards and junkets Melba toast and butter, weak tea and one cup of coffee with milk daily comprise this first part Small feedings are given every two hours during the day together with six glasses of hot water between feedings No ice cold food or drink is permitted during the entire treatment The diet is gradually advanced as distress subsides and normal function is resumed The complete diet used on discharge and for many months or years thereafter is a well balanced one the chief articles excluded being all fried foods pastries all raw vegetables except garden lettuce celery and carrot sticks, all uncooked fruits except orange juice diluted with hot water and all pork products except oven broiled bacon Meats should be beef lamb chicken or turkey and must be broiled or roasted not boiled No candies or nuts nor the notoriously indigestible foods such as baked beans oily fish and condiments are allowed The patient is urged to omit smoking altogether and to use alcohol if at all very moderately well-diluted and without ice Bowel function has usually been restored to normal by the time the patient is discharged from the hospital and instructions are given for the use of oil retention enemas or in case of emergency a saline enema if this becomes necessary at any time These instructions give the patient a sense of security for future contingencies

The restrictions in diet may necessarily be lifelong in some patients who if they are indiscreet in diet may have recurrence of symptoms In others a few weeks of careful adherence to this regimen seems to restore such normal function that a general diet may again be adopted

The habit of regular defecation is usually established gradually but for the accomplishment of this regularity the patient must be instructed not to interfere psychically by conscious efforts Here nature likes to take its course and if the patient can become bowel unconscious he will soon find that stools will be passed fairly regularly but this regularity should not be made a fetish Normal consistency of the stool rather than the frequency or regularity of defecation is the important evidence of good colonic function

In conclusion I should like to emphasize three points first that good colonic function plays a predominant role in the comfort and happiness of the human being and conversely that dysfunction becomes an important issue to the patient and should be so regarded by the physician second that the cause is most often abuse of the colon by the patient and not infrequently by neglect or improper advice of the physician and third that the keynote of treatment is rest applied to the colon in the manner described and adequate instruction of the patient as to what he should expect from that organ

of dysfunction The diagnostic criteria are the rate of speed of filling depth and frequency of haustral markings caliber of colon with presence or absence of spasm or atony, degree of discomfort experienced by the patient (varying from very severe colicky pain with incontinence in the very spastic colon to complete lack of sensation in the redundant atonic type) All these X ray criteria are found after successful treatment to be changed to more normal findings A finding of great interest is the anatomical contour of the splenic flexure If this is high and directly under the diaphragm, symptoms of distress in the left upper quadrant and even palpitation from subdiaphragmatic pressure are often explained on the basis of trapped gas in this high flexure Proctoscopy usually shows a glary mucosa often with excessive amounts of mucu coming down into the field of vision

For assurance of both physician and patient organic disease in the digestive tract must be found or ruled out and the patient treated accordingly It is equally important that in the presence of other disease in the digestive tract such as gallstones, peptic ulcer or diverticulitis a coexisting functional colitis be adequately treated Otherwise there will be confusion and inadequate results in the treatment of the organic condition and an unhappy patient who considers his operation or medical treatment for the organic disease a failure

The causes of functional colitis are, in my experience of two types distinct or intermingled The psychogenic which operates alone in certain cases is transient in effect and often recognized by the patient In such cases psychotherapy if successful cures the digestive as well as the psychic disorder The other type is somatic and operates for two reasons either because the psychic cause is no longer transient but has become habitual and therefore establishes a habitual somatic dysfunction or because the somatic disturbance is caused by abuse of the digestive tract with incorrect diet alcohol or smoking excesses or most often by the habitual use of laxatives and their equivalents In certain cases the result of this abuse operates somatopsychically and we have an interplay of bad digestive habits and resulting apprehension

The treatment of functional colitis is based on that most effective aid of medicine rest The colon must be considered tired and abused not lazy or obstinate and if adequate measures are taken to rest it natural function can usually be restored In cases of prolonged dysfunction or severe distress and distention bed rest in the hospital is both necessary and justified This is true because the resumption of a normal diet and routine of living can then be made gradually and under observation of the patient s condition Rest in bed rest to the digestive tract through bland diet heat applied to the abdomen on and off systematically during the day antispasmodics supplementary vitamins very mild sedation when necessary and as much mental rest education and encouragement as is possible are the mainstay of this therapy Cases of constipation even of many years duration usually yield to this treatment Temporary aids for constipation may be necessary at first and if so small (three ounce) retention oil enemas are used or occasionally saline enemas of one to three pints No medication with any laxative effect (and this includes mineral oil and bile salts) is permitted The diet is divided into six parts part one being used exclusively at first White cooked cereals such as cream of

develop with use of hexamethonium orally We are fortunate indeed, that most patients have intestinal tracts which perform their subconscious function capably throughout life unassisted by patient or internist Very few patients need surgical aid in this connection

Although the sympathetic and parasympathetic nerves usually play only accessory or regulatory roles in gastrointestinal motility, there are circumstances in which these nerves can alter or disrupt function as a result of stress originating in the central nervous system Several examples have been presented by preceding papers Traumatic ileus is one example of stress encountered not infrequently by surgeons FIGURE 1 illustrates distention of large and small intestine by gas The patient slipped on an icy walk two days before the roentgenogram while carrying a bucket of coal He experienced some back pain The major complaint was abdominal discomfort and distention accompanied by nausea Motility is disorganized not arrested Borborygmus is conspicuously audible Spontaneous recovery occured the following day

The subject Congenital Obstipation from the surgical point of view requires consideration of Hirschsprung s disease or magacolon Surgeons have long been aware that the chronic obstruction of fecal fistula following improperly repaired imperforate anus causes a large hypertrophied and impacted colon The etiology of megacolon is more obscure When colostomy is performed for either condition the large colon returns to normal size Surgeons have accordingly not felt that the conspicuously dilated bowel exhibiting huge



FIG 1

CONGENITAL AND ACQUIRED SERIOUS OBSTIPATION*

By Keith S Grimson

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The first five papers of this monograph have developed excellently the physiological pharmacological and structural behavior of the colon, while the two succeeding papers have introduced important medical considerations In this present paper, I shall deal with several observations made by use of surgery other than that for tumor, or by use of autonomic blocking drugs Surgeons are well aware of the propriety of managing constipation by diet or drugs and do not regret that they seldom need enter this field

Operations on the sympathetic and parasympathetic divisions of the autonomic nervous system have demonstrated that the gastrointestinal tract is largely independent of its extrinsic innervation as it carries on its anabolic and excretory function Primary motor function depends upon the myenteric plexus of Auerbach and Meissner

Total sympathectomy[1] in patients with hypertension does not produce any clinically important changes of gastrointestinal function Bowels move daily Vagotomy without gastroenterostomy[2] produces some change, conspicuously failure of strong propulsive peristalsis of the pylorus and resulting faulty function of the ejection cycle faulty opening of the pyloric sphincter and poor gastric emptying This results in gastric retention After vagotomy the usual motor activities of the esophagus and gastric cardia continue The motility of the small intestine is occasionally slightly altered Diarrhea occasionally developed following vagotomy alone One cause was spoiling of food stuff retained in the stomach Vagotomy with gastroenterostomy avoids gastric retention and such diarrhea but occasional patients particularly when nervous or worried have episodes of diarrhea not associated with weight loss The usual change for ulcer patients is from constipation before vagotomy and gastroenterostomy to normal bowel habit afterward Parasympathetic denervation of the colon occurs as a result of spinal cord injury The defecation reflex is handicapped much like the specialized function of the pylorus after vagotomy Less specialized motor functions of the colon continue

It is therefore evident that the gastrointestinal tract when deprived of its central connections through the autonomic nervous system carries on its rhythmic movements capably Only when the intrinsic plexus is slowed down by continuous use of curariform drugs Banthine or hexamethonium can marked depression or arrest of rhythmic movements and associated troublesome constipation occur Even with these drugs this troublesome side effect is not too bad By use of laxative diet laxatives or cathartics treatment can be continued to accomplish the desired therapeutic results for ulcer or hypertension The occasional intriguing independent and often perverse nature of colon behavior is emphasized by the fact that diarrhea rather than constipation or alternating diarrhea and constipation without impaction occasionally

* Th wo k report d h w pport d by grant f om th D on f R h G t d F ll w h p of th N t on l In tit tes f H lth U S P bl H lth S rv

avoidance of hard round orange to grapefruit sized impactions of stool which otherwise occur in the dilated segment Eventually these impacted masses dilate the normal sized segment and present at the anus much as a fetal head during labor However they can be broken up by manual manipulation as they occur and episodes of distention thus avoided In some patients this office procedure manipulation is required every few months After some in conveniences during childhood these patients in our continuing experience usually dilate to the anus and have little if any trouble in adult life

This Group III sigmoid type of megacolon or sigmoid achalasia as it has been called may first present itself with enlarged abdomen and troublesome symptoms Segmental resections have been done for it in the past Swenson and others have explained the sigmoid achalasia phenomenon as absence of the myenteric plexus in the normal sized distal segment of sigmoid and the rectum. The idea of absence of peristalsis and the term achalasia date back to the studies of Hurst[6] As early as 1913 Hurst demonstrated that there was no spasm in cardiospasm of the esophagus

Resemblance between the derangement of function of the lower esophagus with dilatation of the upper esophagus and the similar derangement of some types of megacolon have often been referred to in literature (witness the term mega-esophagus) Bull[7] in 1925 credited earlier reports of Hacher and Bard with the suggestion that dilatation of the esophagus might be a congenital mal formation similar to megacolon or Hirschsprung s disease Our studies follow ing esophagogastrostomy[8] performed for nine patients with massive enlarge ment of the esophagus revealed that slowly 7 to 53 months the enlarged portion reduced to normal size in four and to almost normal size in two patients This observation parallels result of colostomy in megacolon although the re turn to normal size is slower and less consistent Destruction striking loss or complete absence of the ganglion cells of the myenteric plexus was demon strated for achalasia by Rake[9] in 1927 and Lendrum[10] in 1937 Our histological studies of the plexus in achalasia and in megacolon were handicapped by diffi culties of staining technique Negative demonstrations occasionally occurred in control normal colon specimens and in nondilated or test specimens from megacolon Parasympathomimetic drugs however induced some activity in these nondilated segments as judged by balloon studies We therefore refer to an abnormally functioning normal sized lower sigmoid and rectum in mega colon rather than to an inert or spastic segment Our clinical management differs from others who recommend rather routine operations using pull through techniques

For sigmoid achalasia we recommend careful medical management without operation Results to date seem to have warranted this conservatism A late follow up of nine patients Group I indicates good results in eight there having been one death following a sympathectomy which had been performed in 1938 Of 16 patients Group III each has had a good result six by spontaneous improvement and nine by medical management plus bethanechol chloride One patient developed volvulus requiring surgical reduction and has since been all right.

strong visible peristaltic waves is the site of the disorder Enlargement is the result of obstruction and impaction

Colostomy is reserved for emergency problems only Better methods of management of chronic problems have been sought Bruening, in 1925[3] probably performed the first "pull through operation for megacolon He resected the entire colon and rectum, and the terminal ileum was pulled through the anus Segmental resections of colon usually sigmoid colon have been recommended by Finney, Dixon Ravitch, and many others Sympathectomy received extensive trial Our reports in 1944[4] and 1945[5] helped to discard sympathectomy This procedure was ineffective It was dangerous as well because of associated interruption of abdominal pain sensation Patients were not warned when impaction occurred and impending strangulation or peritonitis threatened

My first contact with the serious obstipation of megacolon occurred in 1943 Prior to this time surgery had been declined for most patients because of belief that good medical management was preferable My first contact with serious megacolon occurred in 1943 in a university student aged 21 In childhood he had obstipation and persistent distention In 1943 he had a gigantic abdomen but was emaciated otherwise Since sympathectomy seemed absurd he was explored with interest as to the cause of his megacolon and in the hope that something could be done The huge colon converted abruptly into a grossly normal sigmoid stump at a point five inches above the pelvic floor It seemed logical to resect this hypertrophied colon anastomose the terminal ileum to the normal sized stump of the sigmoid and thus empty the liquid content into the lower sigmoid and rectum This procedure worked well The patient developed normal physique and during eight years since the operation has had one to four bowel movements daily

The studies of 24 patients[4, 5] previously observed with megacolon in either the clinic or hospital were then undertaken Original and subsequent roentgenograms proctoscopic examinations barium and air contrast studies indicated that three separate types of megacolon pathology had been encountered The first Group I included 12 patients who had uniform involvement of all of the colon and a dilated or easily dilatable rectum The second Group II included seven patients who had uniform dilatation of the proximal colon terminating in the sigmoid region in a normal segment of sigmoid colon and a normal sized rectum The third Group III included five patients who had enormous dilatation of the upper sigmoid and descending colon with or without some dilatation of the proximal segments and a normal or dilated lower sigmoid and rectum Follow up studies reveal that medical management had been sufficient for Group I patients We recommended strong cathartics only once a week and enemas at midweek intervals thus avoiding continuous use of mineral oil or of daily laxatives which have a constipating effect When bethanechol chloride Urecholine Chloride became available five tablets 25 mgm were given orally each morning and three tablets 15 mgm midmorning and midafternoon This has aided conservative management Group III patients were similarly managed medically except that added emphasis was given to

avoidance of hard round orange to grapefruit sized impactions of stool which otherwise occur in the dilated segment Eventually these impacted masses dilate the normal sized segment and present at the anus much as a fetal head during labor However they can be broken up by manual manipulation as they occur and episodes of distention thus avoided In some patients this office procedure manipulation is required every few months After some inconveniences during childhood these patients in our continuing experience usually dilate to the anus and have little if any trouble in adult life

This Group III sigmoid type of megacolon or sigmoid achalasia as it has been called may first present itself with enlarged abdomen and troublesome symptoms Segmental resections have been done for it in the past Swenson and others have explained the sigmoid achalasia phenomenon as absence of the myenteric plexus in the normal sized distal segment of sigmoid and the rectum The idea of absence of peristalsis and the term achalasia date back to the studies of Hurst[6] As early as 1913 Hurst demonstrated that there was no spasm in cardiospasm of the esophagus

Resemblance between the derangement of function of the lower esophagus with dilatation of the upper esophagus and the similar derangement of some types of megacolon have often been referred to in literature (witness the term mega-esophagus) Bull[7] in 1935 credited earlier reports of Hacher and Bard with the suggestion that dilatation of the esophagus might be a congenital mal formation similar to megacolon or Hirschsprung s disease Our studies follow ing esophagogastrostomy[8] performed for nine patients with massive enlarge ment of the esophagus revealed that slowly 7 to 53 months the enlarged portion reduced to normal size in four and to almost normal size in two patients This observation parallels result of colostomy in megacolon although the re turn to normal size is slower and less consistent Destruction striking loss or complete absence of the ganglion cells of the myenteric plexus was demon strated for achalasia by Rake[9] in 1927 and Lendrum[10] in 1937 Our histological studies of the plexus in achalasia and in megacolon were handicapped by diffi culties of staining technique Negative demonstrations occasionally occurred in control normal colon specimens and in nondilated or test specimens from megacolon Parasympathomimetic drugs however induced some activity in these nondilated segments as judged by balloon studies We therefore refer to an abnormally functioning normal sized lower sigmoid and rectum in mega colon rather than to an inert or spastic segment Our clinical management differs from others who recommend rather routine operations using pull through techniques

For sigmoid achalasia we recommend careful medical management without operation Results to date seem to have warranted this conservatism A late follow up of nine patients Group I indicates good results in eight there having been one death following a sympathectomy which had been performed in 1938 Of 16 patients Group III each has had a good result six by spontaneous improvement and nine by medical management plus bethanechol chloride One patient developed volvulus requiring surgical reduction and has since been all right.

Three additional Group II problems have confronted us since 1943 seven in all among the present 36 megacolon patients The three also required colectomy and ileosigmoidostomy Of the seven, three were seen in the clinic before use of this operation and each died Of the four treated surgically one has since died This patient female age 26 months had a normal sized lower sigmoid segment nine inches long In the interest of conserving function the entire length of normal sized colon was left in place and the proximal distended colon and cecum were removed Early result of the operation was good with return of nutrition to normal However death occurred three years later by partial obstruction caused by a small mass of impacted stool in a diverticulum which had developed in the long normal sized segment of colon If the same circumstances were again encountered I should resect this normal sized seg



Figure 2

ment along with the colon to a point three or four inches above the floor of the pelvis The remaining three of the four patients are now living and well having one to three bowel movements a day Their nutrition is good

Each of the four patients treated by colectomy and ileosigmoidostomy experienced occasional episodes of abdominal colic and gas without nausea or distention Roentgenograms revealed some accumulation of gas within the terminal ileum and a moderate but not progressive enlargement It is well known that that ileocecal valve is important to the excretory function of the colon Following removal of this valve gas and liquid content tended to regurgitate so that the terminal ileum made a partial reservoir to supplement that of the short stump of sigmoid and the rectum Perhaps a better operation for Group II megacolon would be one anastomosing a short segment of the cecum to the short stump of lower sigmoid thus preserving both ileocecal valve and rectum

Acquired serious obstipation other than megacolon is also usually a medical problem However I should like to present for consideration two patients in whom surgery seemed indicated Each had difficult obstipation

The first a male aged 36 was admitted having a diagnosis of recurrent obstruction of the small intestine A ruptured appendix had been removed at age 14 At age 21 a surgeon performed an exploratory laprotomy for adhesions Thereafter the patient was constipated At the age of 22 he was hospitalized for three days and received repeated enemas Complaints were nervousness and insomnia as well as abdominal distress and constipation A barium enema was obtained and revealed some redundancy of the colon (FIGURE 2) Gas distended the colon but not the small bowel The patient was then repeatedly admitted to other hospitals with similar or more troublesome episodes of obstipation distention and vomiting Six operations for intestinal



F 3

obstruction and adhesions were performed and there were other admissions for intubation decompression therapy and enemas Fistulae had developed from the small intestine following the last two operations The last surgeon wisely stated that adhesions were too bad and that he could do no more

The patient was then referred back to this hospital shortly after an episode Ileal studies revealed normal transit time A conservative program was outlined but four months later obstipation distention and vomiting recurred and persisted during 21 days of hospitalization Again X rays revealed distention by gas in the colon (FIGURE 3A) The small bowel was not distended Redundancy of the colon was demonstrated by incomplete barium enema (FIGURE 3B) Redundancy had markedly increased during the 15 year interval following the roentgenogram of FIGURE 2 The barium in the left colon (FIGURE 2B) remained there one week in spite of cathartics, large and frequent doses and enemas four times a day The patient then had partial evacuations and somewhat improved He returned to the hospital three weeks later again in trouble distended and passing nothing by the rectum Again there was distention of colon not small bowel (FIGURE 4A) The six preceding operations had evidently been directed to the wrong cause Partial colectomy seemed indicated Operation was carried out resecting 24 inches of colon mid transverse to low sigmoid FIGURE 4B shows the post operative barium enema The patient during 19 months of subsequent observation has had normal bowel movements interrupted by two or three short periods of diarrhea and has gained weight and strength

The second patient aged 57 had been constipated all of his life and the difficulty had gradually increased Numerous roentgenologic studies and several barium enemas had revealed remarkable elongation and redundancy of



FIG 4



Figure 5

the colon but no suggestion of dilatation resembling true megacolon. A … er experiences a similar problem and has similar X-rays for l… For 30 years the second patient had taken two-and-one half quart enemas two to four in succession for bowel movements which he thus achieved every three to seven days. Numerous laxatives had been used, but were not effective. He experienced much discomfort and usually felt distended although the abdomen was not large.

Several physicians had been consulted but surgery had not been advised until two months before his referral. Then an emergency cecostomy was done because of failure of movements in spite of his enemas and the occurrence of signs of peritoneal irritation. Decompression was difficult. When he was admitted the colon had been decompressed. A partial colectomy was performed removing 41 inches of colon. FIGURE A shows the postoperative barium enema when filled and FIGURE B the same enema after evacuation. The anastomosis is in the upper left quadrant of the abdomen. The remaining right colon empties freely. During three years and five months of postoperative observation, this patient has felt well and has improved in weight and appearance. Bowels move every other day and he has no sensation of distention.

Studies of the myenteric plexus were not obtained in either patient. However, marked delay of emptying and progressive elongation of the colons before operation and definite delay of emptying of the proximal segment of the shortened bowel after operation suggests that a serious motility disturbance existed.

Conclusions

(1) Surgery is usually not necessary for patients having megacolon When indicated (Group II patients) removal of enormously dilated colon and cecum has effected satisfactory results with preservation of the rectum Preservation of the ileocecal valve might have avoided the occasional episodes of accumulation of gas in the terminal ileum

(2) Surgery is usually not necessary for patients having progressive constipation However when serious trouble occured in two patients resection of long segments of colon preserving rectum and ileocecal valve restored bowel function

(3) In megacolon and in severe constipation varying degrees of motor dysfunction occur Abnormal or decreased activity rather than absence of activity or spasm have been observed

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LIFE STRESS AND CHRONIC ULCERATIVE COLITIS*

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The relationship between periods of emotional stress and the onset and exacerbation of symptoms in patients having chronic ulcerative colitis has been well established In addition distinct personality features and behavior pattern have been found in these patients[1 2 3 4] Aside from the work of Lium[5 6] little experimental work has been done to clarify the physiological mechanisms through which such a disease process comes about in human beings

A unique opportunity to study the function and behavior of the human colon was presented in four fistulous subjects (FIGURE 1) Subject A who was observed daily for eight weeks was a 26-year old man who had ulcerative colitis for six years and had had a large prolapse of ascending colon and cecum through an old cecastomy wound Subject B studied daily for four weeks was a 54 year-old plumber had a large prolapse of descending colon and sigmoid through a left colostomy wound Subject C † who was observed twice weekly for eight weeks was a 44-year-old business man who had a small prolapse of cecum through a cecastomy wound Subject D a 67 year-old broker had a large prolapse of transverse colon through a transverse colostomy This subject was observed daily for two weeks

Methods

The motor activity was observed and photographed by still and motion pictures In all subjects colonic intralumen pressure changes in an inlying inflated balloon were recorded on an ink writing kymograph When possible simultaneous recordings were made from areas in both the ascending colon and the descending or sigmoid colon

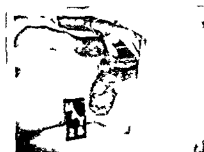
Blood flow Color readings were recorded by comparing the color of the mucosa to an appropriately graded color scale standardized according to the method of Munsell[7] That color changes predictably reflect changes in blood flow has been demonstrated by Richards Wolf and Wolff[8] In general the redder the membrane the greater the blood flow

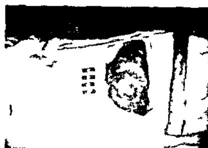
Lysozyme Lysozyme concentration in the secretion removed directly from the surface of the mucosa was measured by the viscosimetric method of Meyer[9]

Secretion Secretion was observed to be present on the surface of the colon at all times When it was scant in amount it was designated as one plus When the secretion was so abundant as actually to drip from the surface of the bowel it was designated as four plus Two and three plus were applied to conditions between these extremes

Fragility The fragility of the mucous membrane or its reciprocal resistance to injury was measured by applying negative pressure to the mucosa The

* Th w k report d h w pport d p b f d f om th Commonw lth F d
† Th bse tio d d Subj C w re m d by th th wh n h w l l t t t th g t tes f phy l g l se h t f th M t S Hosp tal i th d t f Doc o R ph k fma Doc d cy M g l Doct Ash W k Lt d Doct F kl H ll d


SUBJECT A


SUBJECT B


SUBJECT C


SUBJECT D

F URE 1 Ph tograph h g th l t s d sh r f th c l c p ol p th f fi t l
[illegible]

instrument consisted of a soft rubber catheter a mercury manometer and a syringe. A known pressure was exerted for an arbitrary number of minutes. If this injury did not produce a small petechial lesion then either the pressure or duration of application was varied until a sufficient force was applied to produce such a lesion.

The subjects were customarily observed at the bedside or in the laboratory one and one half to two hours after the last meal. Observations of motility color and secretion were noted after the patient had been resting comfortably and had been lightly diverted for about 30 minutes. Specimens of surface secretion were removed for lysozyme determination and the fragility tested. Each day a short interview was conducted in order to ascertain the predominant mood and feeling state of the patient and to determine what events of significance had taken place in the patient's life since the last observation.

Results

During periods of relative calm and tranquillity the bowel in all four subjects was found to be pale in color (yellowish red corresponding to 30 on the scale) relatively immobile slack scanty mucous secretion thin watery and scanty in amount and the lysozyme concentration in the mucous secretion was

low During phases of anger and resentment the bowel was redder (color varying from 60 to 90 on the scale) hyperactive engorged covered with a thick opalescent tenacious mucus and the concentration of lysozyme relatively high The following are a few typical examples

Subject 1 Day to day existence in a sheltered hospital environment is often productive of emotional calm and tranquillity However even such a circumstance may be productive of emotional conflict On March 1 1948 the subject arrived at the laboratory, grim taciturn and having a slightly flushed face The bowel was hyperactive quite red (60) and engorged and the lysozyme concentration was high (55 units) The surface was oozy and glistening Even gently touching the hypermotile bowel elicited a strong contraction He reluctantly revealed that on the preceding day he had been visited in succession by three physicians who removed his dressing looked at the lesion and then abruptly walked off without saying a word to him He was embarrassed and humiliated by this behavior and reacted with anger and resentment He was in conflict as to whether to complain about this deportment or not Characteristically he said nothing and was still seething with anger when he was observed the next day

On March 4 three days later the subject was brought to the laboratory one and one half hours late for his appointment He was quiet noncommunicative slightly flushed He was loath to remove his bathrobe Contrary to his usual neat appearance he looked dishevelled and unshaven and his hair was hurriedly combed The dressing over the lesion was soiled crusted and falling off Only after considerable discussion with him was it possible to learn the circumstances Owing to a confusion in orders the nursing staff was not informed that he was to be brought to the laboratory this day and after an early breakfast he was allowed to sleep again About an hour later the mistake was realized and he was hurriedly awakened rushed into his robe pushed into a wheelchair and whisked over to the laboratory in spite of his protests over his dressing shaving and washing This was a deplorable situation to this very fastidious man It was the first time he had even been seen in the hospital in such an ill prepared state and was unable to accommodate himself to this embarrassing situation He reacted with anger and resentment but characteristically made no complaints and indeed made feeble excuses for those responsible The membrane was reddened (60) hypermotile the lysozyme concentration 80 units and mucous secretion was thick abundant and tenacious

Subject B The usually placid Subject B came to the laboratory on April 10 1948 obviously angry because of a conflict with the nurses During the previous night he had soiled his bed linen by the involuntary passage of a stool He regarded this as an unfortunate accident The overburdened nursing staff criticized him severely He was embarrassed and humiliated and reacted with suppressed anger and resentment When seen a few hours later he was still angry The colon was hyperemic (color 60) engorged and unusually susceptible to injury The lysozyme concentration was 11 (on a usual day of calm it was 1 unit or less)

Subject C During phases of good spirits cheerfulness, and feelings of calm and security the exposed colon was pale (30) immotile and secretion was thin and watery Lysozyme concentration ranged from 1 0 to 3 6 units per cc During periods of conflict anger or resentment the bowel was redder (50 to 60) more active and secretion was thick and tenacious Lysozyme ranged from 8 to 16 units per cc For example, on December 29th, he was angry, resentful and had hostile feelings toward a physician who had requested him to come into the hospital for additional experiments He was in much conflict as to whether he should or should not comply The patient felt that he was being 'pushed around At the same time he felt obligated to that physician and that he (the patient) should be a "good sport about it The colon was red (60) and hypermotile Secretion was thick and opalescent Resistance to trauma was reduced (FIGURE 2)

Subject D On February 5 1949 the patient was seen at the bedside He was angry Just a few minutes before he had been visited by his former physician, the one who was responsible for giving him streptomycin and thus causing him to be incapacitated because of vertigo He blamed this physician for his loss of equilibrium feeling that the latter had failed to recognize the early signs of toxicity and that the physician had he done so could have prevented the damage to his equilibratory apparatus The patient had forced himself to be polite to him To the author he began a bitter tirade against the physician becoming more angry and resentful It s all his fault ' 'What did he come up here for anyway I should sue him for everything he s got' During this outburst of temper there was a reddening of the bowel mucosa from 50 to 70 and marked increase in its motor activity The mucosa became engorged and small turgid folds stood up on its surface During this time the secretion increased from one to three plus and gas was passed from the colostomy stoma

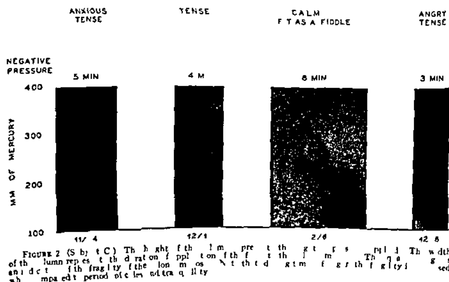


FIGURE 2 (S b t C) Th h ght f th l m pre t th g t f s pl j Th width of th lumn rep es t th d rat on f ppl t on f th f t th l m Th g s of th lumn rep es t th d rat on f ppl t on f th f t th f Th fragility f the lon m os N t th t d g t m f g r th f g l ty i sed an i d c t f th frag l ty f the lon m os wh mpa ed t period of c lm nd tra q ll ty

Alterations in the integrity of the colonic mucus membrane Wolf and Wolff[10] noted the spontaneous occurrence of minute submucosal hemorrhages in association with protracted and sustained feelings of hostility resentment and anger The membrane displayed the appearance of superficial gastritis In the colon through the sigmoidoscope Dennis has observed petechial lesions in patients with ulcerative colitis during anger[11]

Observations on Subject A Under circumstances of relative calm security and relaxation, the colonic mucous membrane was free of petechial lesions After three days of sustained anger and feelings of hostility, however there was observed a profuse eruption of petechial lesions on the exposed segment of colon of Subject A These lesions lasted for only 24 hours For the three days previous to the appearance of these lesions the patient had been in a state of sustained anger resentment and hostility over a series of distressing and humiliating experiences associated with his transfer from one hospital to another He was embarrassed and humiliated by the red tape and pushing around and reacted with his usual suppressed anger and resentment He said nothing to anyone about his feelings and remained smiling and affable throughout

Observations on Subject C During periods of relative calm and security (this patient rarely if ever seemed tranquil) the membrane showed a few petechial lesions These were pin point to pin head sized and had a yellow center It was estimated that about 5 per cent of the mucous membrane was covered with these lesions

During a phase of anger and resentment precipitated by conflict over his wife s attitude toward him many more petechial lesions appeared and it was estimated that about 90 per cent of the mucosa was covered by them These feelings and lesions persisted for about two weeks and gradually subsided Their disappearance coincided with increasing feelings of security and well being brought about by an improvement in his relations with his wife and her improved health and disposition

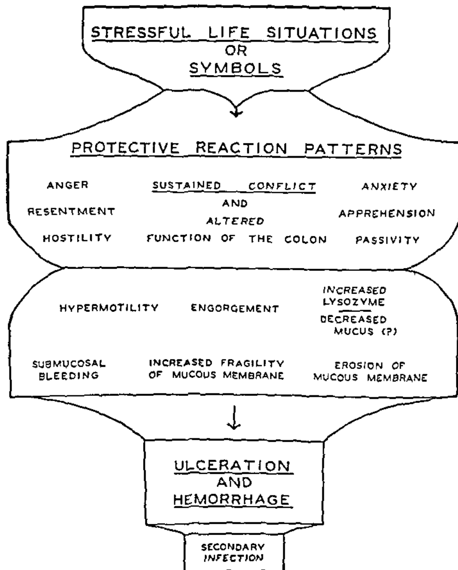
On December 29 numerous petechia again appeared For three days the patient had been increasingly angry and resentful at another physician whom he felt was insisting that he (the patient) enter the hospital for further experiments

At this time he was given reassurance and emotional support and allowed to verbalize his hostility He became calm and tranquil after this interview Forty eight hours later no petechiae were visible

Comment Although these lesions promptly disappeared following the expression of emotion it is fitting to consider the ultimate outcome if the sustained hyperfunction had been allowed to continue Lium was able to produce petechiae and ulcerating lesions in the colonic mucus membrane transplants in dogs His method consisted in eliciting sustained hyperfunction of the bowel either by trauma or by drugs (intravenous prostigmin and local acetylcholine) or by intravenous dysentery toxin He concluded that sustained contraction of the bowel resulted in engorgement and the ultimate ulceration of the mucous membrane In the subject reported here sustained anger hostility and resentment elicited sustained hyperfunction of the bowel This protracted hypermotility and engorgement resulted in the formation of petechiae Had this

situation of resentment and anger been allowed to go on it is likely that the local bleeding and tissue anoxemia would have gone on to tissue necrosis sloughing, and the formation of ulceration

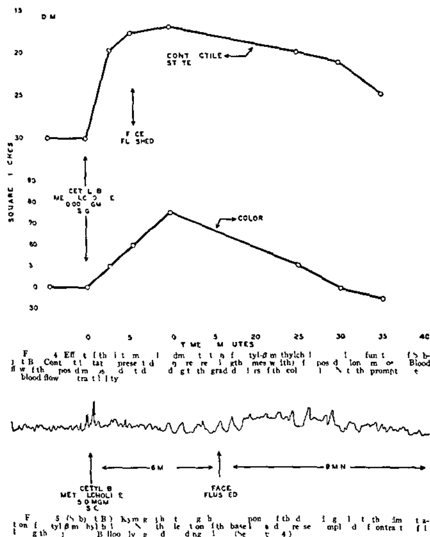
Fragility of the mucous membrane By using the method previously described for estimating the fragility of the mucous membrane or its reciprocal resistance to injury wide variations have been demonstrated (FIGURE 2) If, accordingly, the height of the column represents negative pressure in mm of mercury and



Ft u e 3 D gramm ti repre tat of th m ch m f p od t f l m os l on re lt of l hyp rfun t

the width of the column represents the duration of application of this pressure then the square area enclosed gives an estimate of the force necessary to produce a small hemorrhagic petechial like injury Observations on Subject B show that to produce a lesion during periods of calm security, and relaxation pressures of about 200 mm of mercury had to be applied from four to eight minutes whereas during phases of anger resentment and hostility (i e the day on which the subject soiled his dressing) only 60 mm of mercury had to be supplied for one and one half minutes

Alterations in lyso yme concentration Feelings of anger resentment and

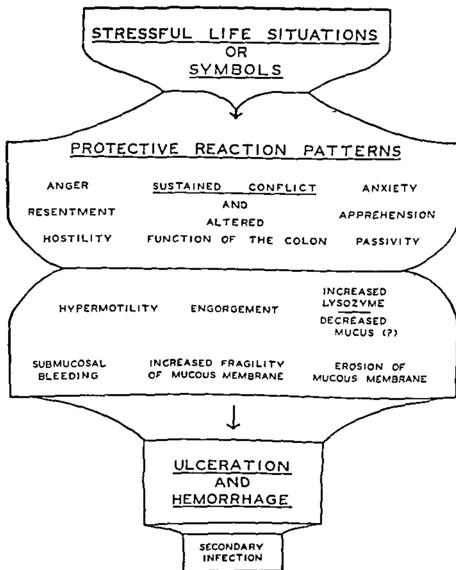


F 4 Eff t f th i t m l dm t t n f tyl-β m thylch l l fun t f S b-j t B Cont t l tat prese t d n re re l gth mes w ith f pos d lon m or Blood fl w f th pos d m s d t d d g t th grad d l rs f th col l t th prompt e blood flow tra t l ty

F 5 (S b) t B) Kym g h t g b pon f th d i g l t th im t a-t on f tyl β m hyl h l th le t on f th base l s d re se mpl d f ontra t f l g th j B lloo ly g d d ng l (Se t 4)

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Fi t 3 Dagramm t r p s nt t n f the m b m f p od t f lon m os le s r lt f l hyperfun t

the secretion of a thick tenacious mucus has been observed in all of our fistulous subjects during periods of anxiety or anger We believe that the engorged mucosa and the continued hyperfunction lead to submucosal bleeding and ultimately to ulceration Finally the increased lysozyme may contribute to the damage by eroding the mucous membrane The engorged fragile, eroded mucous membrane is probably easily invaded by indigenous fecal microorganisms or is further damaged by the action of substances normally present in the fecal stream This thesis is shown diagrammatically in FIGURE 3 The work of Wener and Simon [15] producing ulcerative colitis in animals, was done by the prolonged administration of mecolyl This agent produced hyperfunction of the colon in our Subjects B and C[16] (FIGURE 4)

Conclusions

(1) Feeling states characterized by anger and resentment are associated with hyperfunction of the colon This hyperfunction of the colon is manifested by hyperemia engorgement hypermotility hypersecretion of mucus and of the enzyme lysozyme

(2) Hyperfunction of the colon results in increased fragility of the colonic mucosa

(3) The colon during periods of anger and resentment resembles the colon after the administration of mecolyl

(4) Sustained feelings of anger and resentment associated with sustained hyperfunction of the colon result in submucosal bleeding and ulceration

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hostility are associated with a hypermotile, engorged colon Under these circumstances lysozyme concentration is high[12] The injurious effect of the application of high concentrations of lysozyme to the surface of the colon has been shown[1, 13] That the effect of lysozyme on the intestine which is fragile or engorged is more deleterious is certainly highly probable

Ulceration of the mucous membrane Just prior to the beginning of our observations Subject A was convalescing from an acute exacerbation of his ulcerative colitis which occurred in a setting of protracted resentment over the fact that his brother had started to live with the sister in law after they had been separated for many months He was angry that the brother was going to take up with her again and visualized fresh humiliations for himself and other members of the family and further anxiety lest the sister in law move back into the patient s house His difficulty culminated when he gained the impression that an acquaintance was spreading rumors about his family in the neighborhood He said he felt like beating him but instead only seethed with anger and resentment for the next few days At this point his bowel was noted to be very red with a thick yellowish discharge from the stoma After hospitalization the discharge stopped and the bowel became less red but approximately two weeks later there were still several small shallow ulcerations 1/8 to 1/4 inch in diameter scattered about the surface of the prolapsed mucosa After approximately a week of observation when he had established a good relation with the author and felt secure in his environment relatively cheerful, happy and relaxed the ulcerations greatly diminished in number

Relative prevalence of colonic hyperfunction The colon of Subject A, who had ulcerative colitis was relatively hyperemic (color higher than 40) more than 50 per cent of the time while such redness was observed in Subject B only half as frequently Lysozyme concentration in the bowel secretion of Subject A was high (over 25) in 80 per cent of the day to day determinations while an elevation of lysozyme concentration to 11 occurred only once over the three week period of observation in Subject B Compared to days of calm and security when the bowel was pale and slack Subject A s bowel was in a state of exaggerated contraction about half of the time A contracted bowel was seen on only one occasion in Subject B Subject C who had ulcerative colitis likewise showed a reddened hyperemic colon more than half of the time of observation Subject D who was in low spirits and dejected on each day of observation never showed a contracted bowel Subject A was in a state of serious conflict and had suppressed feelings of anger and humiliation more than 50 per cent of the time in contrast to Subject B who was angry and resentful only once during the period of observation

Discussion

Kymographic tracings were recorded from the sigmoid portion of the colon in a series of subjects with ulcerative colitis These showed either a straight line recording indicating sustained colonic contraction or a rise in the base line of the tracing during feelings of anxiety or resentment indicating a sustained contraction in the sigmoid region[14] Increased rhythmic contractility sustained contractions hyperemia engorgement hypersecretion of lysozyme and

impaired or both The constipation seen in depressed patients is often associated with anorexia and smaller meals It is known from the work of Stewart Wolf[6] that moods of depression resignation and withdrawal are accompanied by diminished gastric motility Grace observing the colostomy of one of his experimental subjects noted that during such moods the ingestion of a standard meal was followed by much less vigorous colonic motility than during relative tranquillity and good spirits[8]

Peristalsis in the colon may be retarded not only by weakness of the wave of contraction but also by failure of receptive relaxation (sometimes called achalasia) or by heightened segmentation movements (usually referred to loosely as spasm) The best understood site of these processes is the sigmoid colon which has been studied *fluoroscopically proctoscopically and kymographically* All the textbooks of radiology show illustrations of a string sign (a narrow thread of barium in the sigmoid and descending colon) indicating obliteration of the lumen in spastic constipation This classic picture seems to have gone out with the five cent fare and is today hard to find Lesser degrees of narrowing of the sigmoid however are probably indicative of the same process

Proctoscopically the constriction of the sigmoid can be most impressively shown Although the rectum is widely patent, in the lower sigmoid there may be an abrupt transition to occlusive spasm so powerful that the instrument cannot be advanced with any reasonable force From below it looks very much like a sphincter Many observers have been inclined to liken it to a sphincter and to suggest that it has such a function to prevent the passage of feces from descending colon to rectum until the time for defecation is at hand

Clearly spastic occlusion of the sigmoid can be due to local inflammation as in diverticulitis or an infected tumor but more often it occurs in anatomically normal colons as an accompaniment of emotional tension The occurrence of constipation has been repeatedly observed at times of life stress which engenders emotional conflict The regularity of this clinical coincidence has been made clear by the painstaking studies of White Cobb and Jones[7] Some years ago Dr Kern Dr Tulin and I tried to reproduce this clinical phenomenon in the laboratory under controlled conditions We observed the sigmoid colon proctoscopically for long periods taking note of its engorgement and its state of contraction When the thoughts of the subject were occupied with neutral topics the bowel was widely patent When the experimenters made the subject angry hostile and defensive the lumen was occluded by a vigorous and sustained contraction[8]

This same relationship has also been studied kymographically using single or tandem balloons passed by rectum[8] The sigmoid motility of resting subjects is constant for the individual over a period of two to three hours When *involved in an emotionally disturbing interview heightened contractions* frequently developed The pattern of these nonpropulsive contractions seems appropriate for retaining feces and suggests that the sigmoid is truly a sphincteric zone overactivity of which is associated with constipation Conclusions regarding the moods or feeling states of individuals are less secure than those based wholly on objective data yet these motility changes observable in the

PHYSIOLOGICAL AND PSYCHOLOGICAL FACTORS IN THE PRODUCTION OF CONSTIPATION

By Thomas P Almy

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To be meaningful, a discussion of the factors involved in the development of constipation must confine itself to man In the study of man in recent years we have become increasingly aware of the interrelationships between psychological and physiological phenomena It is appropriate that these aspects of constipation should be discussed together

The structure of ideas which I shall present is composed of materials of varying strength Some of it is laboratory observation conducted under controlled conditions This work is weakened at times, by the need for subjective interpretation of some signs of emotional tension Many of the clinical observations lack hardness for the same reason but others are objective and so often repeated that they have a certain solidity To give the whole thing a recognizable shape and to distinguish bow from stern I have added some hypotheses of the flimsiest sort Even from the back seats these should be clearly distinguishable for what they are

Constipation in the objective sense means delayed passage of feces Having a bowel movement requires the integration of smooth muscle activity autonomically innervated with skeletal muscle activity involving segmental nerves complicated reflex patterns and suprasegmental control The process divides itself naturally into the mechanisms of colonic motility and those of defecation Delay can occur in either or both of these steps in the process

Colonic motility involves the propulsion of feces from the right colon to the rectum As stated in previous papers most phasic activity in the colon is nonpropulsive the feces moving onward by brief peristaltic rushes which occur infrequently The usual stimulus to such propulsive motility is the ingestion of food or fluids and the pathway is the gastrocolic reflex We may properly doubt that the stomach is an essential receptor in this mechanism because the reflex seems to function after total gastrectomy The efferent pathway is thought to lie in the cholinergic fibers of the autonomic nervous system as atropine or banthine can interrupt it [1] and similar colonic activity can be produced by parenteral acetylcholine or methacholine That the vagus is not the only efferent is indicated by observations of Grace[3] in which the reflex persisted in one of his fistulous subjects after an effective vagotomy

Constipation may develop because the gastrocolic reflex with resulting mass peristalsis, doesn t get started or because it is blocked Fasting man is constipated[4] Marked reduction in the bulk of fluid or food or in its residue diminishes the vigor of peristaltic rushes in the lower bowel Witness the constipation of ulcer patients given only milk and cream Even with normal intake of food, there may be impairment of the gastrocolic reflex owing to diminished gastric motility Constipation is not an uncommon symptom of gastric cancer,[5] in which the food intake is often reduced or gastric motility

by their parents' example that they should not defecate except with the bath room door locked In the highly civilized adult having a well-ordered exist ence the 'negative signals have accordingly multiplied and the positive' signals are few the bowel movement can be had only in the same bathroom after the same breakfast while checking on the same watch to make sure that there is time to make the 8:08 train

Let this same person sleep late on Sunday go to Chicago on the sleeper or go to the hospital for a checkup the 'positive signals being temporarily lacking he fails to move his bowels for varying periods of time This con stipation often continues for a short time after he returns to his former habits until he can reestablish positive conditioning Transient constipation may thus develop out of a wide variety of incidents in our lives In most cases normal habits of defecation are spontaneously resumed after a few days or weeks but for several reasons this resumption may not occur and chronic constipation may be established

Clinically the most obvious reason for transient constipation is the patient s failure to understand the need for regular visits to the toilet and his belief that only a well marked urge to defecate should lead him there In order to produce the desired urge he takes increasingly strong cathartics and gets bowel movements at unfamiliar times and irregular intervals This development further disrupts conditioning The stronger cathartics empty the bowel so completely that more than a day may be required to fill it again This leads of course to their overuse on the premise that a daily bowel movement is best no matter how it is obtained Cathartics also irritate the colonic mucosa to such a degree that considerable spasm of the left colon remains and is easily visible proctoscopically In these patients spasm of the distal colon seems to occur also as an accompaniment of the emotional tension engendered by the constipation itself Repeated failure to normalize bowel function makes the *trip to the toilet a symbol of frustration The original disturbance of con* ditioned reflex behavior thus becomes complicated in many ways and the re sulting constipation is prolonged

There are a number of *less common forms of constipation* in which the mecha nism is somewhat different or is actually unknown Megacolon has already been described by Dr Grimson The constipation induced by *opiates* is associated with an increase in segmental nonpropulsive activity almost every where in the small and large intestines In *lead poisoning* the same effects on the membrane of the muscle cell which produce cramps apparently produce sustained spasm and delayed passage of feces[12] Constipation is common in *hyperparathyroidism* where hypercalcemia may impair the contractility of muscle This seems to be true in skeletal muscle but there is not yet proof that the effects on smooth muscle are clinically important We do not have adequate studies on the constipation of *myxedema* It has been suggested that the force of contraction of smooth muscle is impaired by myxedematous deposits as in the case of cardiac muscle At the same time the patient having hypothyroidism commonly lacks the vigorous appetite which strengthens the gastrocolic reflex and the attention to toilet habits which healthy persons require for optimum bowel function The latter factors are also present in

laboratory seem to be consistently accompanied by feelings of tension hostility, defensiveness tenacity These same attitudes are commonly observed clinically in patients having spastic constipation, and are significantly different from those of patients having diarrhea [9] Pending further evidence, constipation associated with spasm of the distal colon can be thought of as part of a primitive integrated pattern of reaction to stress

When impaired colonic motility is the cause of constipation, the delay occurs at the sigmoid level or higher The rectum is usually empty of all but exceedingly small and hard pellets of feces In other constipated patients however the rectum contains large masses of stool of normal or softer consistency These facts will suggest that, in these cases the rate of passage of contents is normal until the rectum is reached, and that the defect lies in the process of *defecation* This condition is the second major form of constipation, and is best understood by calling to mind the fact that the emptying of the rectum is a reflex phenomenon

In the newborn child, the defecation reflex is quite simple The distention of the rectum by a stool coming from above—or the insertion of a proctoscope from below—leads promptly to relaxation of the anal sphincter and the muscles of the pelvic floor, then to the drawing up of the thighs and the contraction of the muscles of the lower back, the anterior abdominal wall and the diaphragm There is forcible expiration with the glottis closed This reflex is apparently organized at the segmental level by a center in the sacral cord Damage to this center, as in cord compression or to the afferent or efferent nerves as in lesions of the cauda equina may lead to acute obstipation [10] More often the effector muscles are weakened or damaged as the result of multiple pregnancy birth injuries anterior horn cell disease or muscular dystrophy Most commonly, the segmental apparatus is interfered with by painful lesions of the anus, such as fissure or thrombosed hemorrhoid which prevent relaxation of the sphincter

As the child grows this reflex is affected by more and more complex conditioning In the process of toilet training it is first intimated to him that defecation can be willfully suppressed and apparently by trial and error, he learns to tighten the anal sphincter hold himself erect and breathe shallowly with high diaphragms until the rectum can accommodate itself to the distending force As toilet training involves the earliest disciplinary demands ordinarily made by the mother upon the child it seems plausible that by mere association in his experience hostility toward the mother might become related to the process of defecation Psychoanalysts have gone far beyond this point in explaining adult constipation on the basis of conflict situations arising in childhood [11] More numerous studies and more direct observation of the process of toilet training might provide acceptable evidence that these childhood events can affect adult bowel function

Further growth and increasing awareness of social pressures cause the defecation reflex to become negatively conditioned to a wide variety of situations or " signals —the classroom the athletic field or the friend s house The extent of this development varies of course with the taboos of the child s own family some children are taught that all public toilets are dirty or are shown

DISCUSSION OF THE PAPERS

Doctor Asher Winkelstein (*Mount Sinai Hospital New York N Y*) I should like to ask Doctor Prugh whether he implied that ulcerative colitis in the adult is the result of disturbances in bowel management in infancy If he does imply this I should like to hear what he thinks about this prolonged time interval I know that the unconscious is considered timeless but in these cases it seems to take a very long time

With reference to Doctor Jordan s discussion I agree with her that both psychic and somatic approaches are needed in the study of chronic constipation It is my impression that the functional disturbances of the colon commonly called the aerocolon (personally I prefer to use the term hyperirritable intestinal tract) are usually the results of neuroses Whether mucous colitis is an exaggerated state of these conditions or a separate distinct entity remains an unsettled problem

Some years ago Chester Jones and his collaborators demonstrated that mucous colitis is probably a parasympathetic disturbance, chiefly in the nature of the motility of the bowel and the large increase in mucus is secondary to *mechanical irritation due to increased muscular spasm* This question is a point of greater interest particularly in line with Doctor Prugh s observations of diarrhea constipation *etc* occurring from infantile disturbances and bowel management. It seems to me a point of great interest that these various conditions (constipation diarrhea and mucous colitis) are not the forerunners of ulcerative colitis In other words we have not seen—and this is true in the experience of cases such as the Bargen s series— the transition of chronic constipation or chronic functional diarrhea to ulcerative colitis The ulcerative colitis must either be due to a special type of neurosis and perhaps has a different mechanism Personally I suspect that the functional disturbance in ulcerative colitis is on a vascular basis. Doctor Raymond Megibow in our hospital has found a vasoconstriction in 14–15 cases of ulcerative colitis It is also possible that increased lysozyme may play a role in the disease

Referring to Doctor Grace s paper I am quite familiar with his work because one of his four cases was a patient at Mount Sinai Hospital who was studied by Doctor Grace in conjunction with our psychiatric group In this patient we also found very definite evidence of a vascular disturbance The other functions were only slightly altered When this patient was angered particularly by doctors whom he identified with a German army officer who threatened to shoot him when he was a captain in the British Army in World War I he would show a marked congestion of his colonic mucosa and before our eyes petechial hemorrhage appeared

We found that patients with ulcerative colitis who were treated with ACTH or cortisone showed a marked fall in the lysozyme concentration of the stool This has been observed by others particularly by Seymour Gray but in our patients this did not necessarily parallel the clinical improvement It still remains a possibility as Doctor Grace has pointed out that this lysozyme concentration can be altered independently of the amount of inflammatory

psychotic depression, and the common occurrence of rectal impaction both in depression and in myxedema points to the defecation reflex as the focus of trouble

One further question haunts us Is there such a thing as *atonic constipation?* Can constipation occur entirely because of reduced neuromuscular irritability of the colon? This effect was suggested many years ago on the basis of X ray studies indicating delay in the passage of barium or bismuth With accumulating experience the range of normal passage time has seemed broader and these supposed prolongations not significant I do not believe I have ever seen primary atony of the colon, that is, a disturbance unrelated to reduced appetite or food intake defective habits, colonic spasm, or anal complications

In summary I have suggested that constipation involves defects in colonic motility or in the integrated mechanism of defecation, or both Colonic motility is usually disturbed as part of a defensive reaction against life stress which has characteristic emotional colorings and involves diminished gastrocolic reflexes and increased segmental contractions of the distal colon Defecation is a complex conditioned response which is disrupted by even temporary alterations in the habits of daily life Cathartic abuse is important in that it produces colonic spasm and further distorts abnormal habit patterns In most cases of constipation these factors are intermingled in complex fashion

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child is a much more direct one and probably would be much more productive in the long run

In so far as another methodolgical factor goes it is not what you do but the way you do it especially what else you do besides colonic conditioning In the study of these patients it is very important to determine the total maternal or other conditioning of the child and use that to see whether it could influence the colonic condition in the later development of colonic functions This is important because one does see patients certainly ulcerative colitis patients where there has been mental colonic conditioning minimal constipation no constipation or minimal early colonic conditioning and yet these people suffer from these marked disturbances

I can visualize that one mother who has a predominantly healthy attitude toward her child might condition the child early with minimal disturbance while another mother might ignore the colon as such but compulsively condition the child and cause a good deal of colonic difficulty

In Doctor Daniel s experience with about 25 cases at Presbyterian Hospital and in similar cases of my own at least on a superficial level with four long term analytic studies of colitis cases the general incidence of schizoid or psychotic reactions seems to be about one in five This is about 20 per cent which leads some investigators to consider it a predominantly psychotic disorder I think it is very important for gastroenterologists to clear up this point and to encourage further study of patients suffering from milder types of ulcerative colitis This would also be of importance in the actual determination of psychodynamic mechanisms Methodologically ideal cases to study would be those that are midway between mild transitory colitis cases and severe hospitalized cases that present us with a good deal of schizoid and severely neurotic material for study If we studied the intermediate cases which are mildly neurotic, it is possible that some of the psychological mechanisms might be clearer and enable us to distinguish between primary psychological phenomena and the complicated condensed secondary developments that are found in severely sick patients

The only other point I wish to make is that as far as the psychological technique of investigation goes we should by now reach beyond this approach in studying these cases We should study not just one facet of the patient s total reaction but all the facets not only his conscious components but his unconscious components and all the specific environmental factors in a life situation We should study these over a sufficient period of time so that eventually we may be able to quantitate the psychodynamic components in these rather complex disorders

In a rather prolonged study over five years of a case of hypertension in a ballistographic technique I have been amazed to find how complex these various emotions are and how the factors of anxiety come into play in many subtle interrelationships Also as far as psychological factors go we have to go a little beyond these very important initial correlations Fortunately we have convinced most of the medical profession that emotions are of some importance but we have now to ask ourselves considering emotions in terms of meaningful

exudate You will have noticed that two of his four cases did not have ulcerative colitis, that the area of bowel studied was quite normal, and yet these patients showed marked variation of lysozyme under emotional disturbances

According to Karl Meyer and Doctors Janowitz and Grossman lysozyme may be definitely injurious when applied locally to the mucous membrane in the experimental animal and we have seen very little result with the use of antilysozyme agent such as nisulfazole We have not had any experience with Doctor Grace's aerosol therapy

I should like to add another word about Doctor Grace s studies We feel that such studies of the effect of acute, conscious emotional disturbances on bowel movements are of considerable importance in the interpretation of disease states We have the feeling however that perhaps prolonged psychologic investigation of the unconscious by the method of psychoanalysis would parallel physiologic studies of fistula cases and might prove even more productive and important in the interpretation of disease

With reference to Doctor Grimson's paper which is indeed very interesting and important, my only comment is that he started out with the statement that the extrinsic innervation of the gastrointestinal tract is unimportant in its functioning and then he spent the rest of his paper proving the opposite Personally, I think that the external innervation of the gastrointestinal tract is very important expecially in preserving homeostasis under conditions of extreme stimulation

We are very much interested in Doctor Almy s modern version of Hurst s original classification of constipation that is a division into chronic and rectal types of constipation Doctor Almy presented the material beautifully, in terms of modern psychiatric lingo and I think that he is definitely on the right track in that direction In Hurst s experience and in my own I just say that at least half of the patients with chronic constipation have rectal constipation or dyskinesia and these are certainly due either to local diseases or to poor bowel habits As a rule, these are easily controlled We usually see the colonic type and I am in entire agreement with Doctor Jordan that there is a small intestinal hypermotility and then a disturbance of the peristalsis in the colon This group is certainly a manifestation of an underlying neurosis While the usual drug and diet approach in chronic constipation of the colonic type is fairly successful, there are times when there are real difficulties and the psychologic disturbance chiefly in the unconscious mind needs a different approach from the usual drug and diet treatment

Doctor Leon Moses (*Department of Psychiatry College of Physicians and Surgeons Columbia University New York N Y*) I should like to make a few brief comments concerning methodology Regarding Doctor Prugh s excellent presentation his basic approach to the study of these problems is actually the best we have today Unfortunately the psychoanalytic technique as intensive as it is, does not go back to the first second and third year of the patient s life when these very vital early colonic conditionings are supposed to have occurred It is very difficult, therefore to reconstruct in adult patients just what did take place So Doctor Prugh s approach by studying the

child is a much more direct one and probably would be much more productive in the long run

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biological adaptation to what are these emotions related? What are these emotions of fear and anger, unconscious emotions of rage and anxiety? What are these emotions in relation to the individual s economy in terms of basic dependency needs affection requirements, sexual capacities and the basic assertive aggressive potential of one sort or another? In this way there might possibly be found some more psychologic specificity of this disorder

In the investigation of ulcerative colitis I should like to ee the combined intensive studies of a psychoanalyst and a gastroenterologist engaged in all the experiences and facets of the problem

Doctor Karush at Presbyterian Hospital has started something of this sort but unfortunately, has confined himself to brief observations I think it would be very useful to carry out extensive definitive observations

As has been pointed out by Doctor Jordan therapeutic reversibility can be an important research tool in the determination of etiological components in a disease entity One possible technique to determine just how important psychic factors are in ulcerative colitis would be to subject certain types of cases to actual psychotherapeutic reversal controlled as accurately as possible We see cases where people have suffered from the symptoms of ulcerative colitis for five, ten or fifteen years and where the statistical probability of a reversal, in the opinion of the gastroenterologist is less than five per cent It might be possible to subject some of these patients to two or three psychoanalytic reconstructive therapies and see what effect that has on one of these sustained persistent but supposedly organic reversible states If such a case can be reversed and kept in a state of reversal for a period of possibly three to five years it might be exceedingly important in etiological considerations

PANEL DISCUSSION

DOCTOR EDWARD J KEMPF (*Wading River, Long Island N Y*) I should like to comment on the function of the colon on the behavior of the animal in the struggle for life If we place an animal in a frightening situation it runs away, but if we put the animal in a closed situation and frighten it it cannot run away We then often get a very violent and very vile smelling colonic discharge of diarrhea This has been noted in various sorts of animals including dogs rats and monkeys and of course it will also apply to humans

Let us take cases of ulcerative colitis It has been found that if you question a person a little about the conditioning relations in his life he gets angry and there may be a disturbance of the colon This is a fixed situation It is conditioned Perhaps he hates his mother in law That is a fixed situation just as much as if he were an animal in a cage He cannot escape from the situation It is limiting If he can get away from his mother in law say 100 miles or so and not see her any more he will get some relaxation If you get your patient to the hospital treat him very kindly and nurse him along he finally begins to forget the mother in law or the critical father or the critical mother whoever it is in the family close to him or in a business situation who may exert a very critical and hostile attitude towards him He then reacts with fear just like your frightened animal with a marked convergence of nervous reaction rearward and then in his fear he has a compensatory or defensive rage which he cannot express adequately He speaks He cannot get satisfaction but if you listen to him sympathetically and urge him he may get out the whole story He may even get a different attitude toward the mother in law or the father or brother or the business that dominates without going through many years of psychoanalysis This is really a biological phenomenon that runs all the way back through the animal kingdom especially in the mammals It also occurs in birds On diagnosis of the patient we see he is a case of mucous colitis Here is a person who hates somebody in the family very bitterly and cannot escape from that person s critique Your problem is to find out who that critical person is and endeavor to bring about an adjustment in him The chances are you cannot correct the critical person You have to correct the patient s attitude If we should look at some of these cases of emotional colitis from that point of view we could do something very effective

DOCTOR GRACE In regard to clinical management of patients with ulcerative colitis most of us are using the techniques of establishing a good physician patient relationship in order to help increase the security of the individual There is increasing evidence in our own clinic in a group of 40 patients that this method of therapy is better than other methods of therapy that have been devised to date I think the analogy to a trapped individual or animal is quite good One of the first individuals in my experience has borne out this feeling

DOCTOR INGELFINGER I should like to suggest that we be a little bit cautious in drawing too close an analogy between achalasia or cardiospasm of the esoph

agus and megacolon As far as the dilated portion is concerned the conditions are quite dissimilar I speak on the basis of a series of observations made in other laboratories than ours as far as the esophagus is concerned, and more or less on hearsay, with regard to the megacolon The dilated portion in achalasia or cardiospasm of the esophagus indicated propulsive movement integrated propulsive motion As in Hirschsprung's disease or megacolon strong peristaltic progressive waves may be seen That possibly, is one situation where there are ringlike contractions that may sometimes appear It is certainly an abnormal condition

Further, after removal of the nonrelaxing segment, I am told in megacolon the remaining bowel almost achieves normal function After getting around the nonrelaxing segment in cardiospasm, the remaining esophagus does not return to normal function The abnormal dilated portion of the esophagus has a strong spastic contraction response to the administration of mecholyl More data are needed as far as Hirschsprung s disease is concerned but a few isolated individuals have told me that occasionally it does not produce a similar response in the dilated portion in Hirschsprung's disease in the colon, to that produced in the dilated portion in the esophagus

Finally we see patients in somewhat different age groups and we do feel even on the basis of abnormal physiologic studies that the dilated portion in the two conditions is quite dissimilar Therefore, I should hesitate to make any analogy between the two except in a very superficial way

Doctor Prugh Dr Winkelstein raised the question as to whether I felt that in ulcerative colitis in adult life the condition was the result of disturbance in bowel management during infancy I don t believe that it is that simple I think that may be one of the variables involved as I tried to point out but I believe there are many others also The prolonged time interval which he pointed out between the development of the symptoms of ulcerative colitis in adult life which had not previously existed in childhood is of importance, and I am quite sure that, when psychological factors play a role this seems to represent a change in the balance of forces which had not come about prior to this time One learns in the history of adolescent and adult patients with ulcerative colitis that at a particular point some change did occur The patient left home for the first time at the age of 25 perhaps was married, had a child, finally brought herself or himself to bring about a change in the balance of psychic and social forces but with the change coming about felt helpless and dependent All the conflicts which will be described as being present in such people then came to the surface

I have found, interestingly enough that in children with ulcerative colitis if one goes into the cases carefully and works with the mother therapeutically there is a history of previous disturbance of bowel function of mild degree perhaps not impressive enough to be called mucous colitis occasionally slight diarrhea or constipation It seems to be present many times in very subtle form It does not involve the concept of ulcerative necessarily that goes into ulcerative colitis but there are subtle changes there that represent the interaction of the psychologic and biologic forces that I mentioned Michaels and some other people put forth the concept in individuals with ulcerative

colitis of other sweeping disturbances of psychologic or physiologic functions. There are cases of a psychologic biologic infantilism, these are fragile persons who have certain equipment that plays a role, once the balance of psychic forces is brought about

In regard to the statement Dr Moses made I should certainly like to say that I appreciate his pointing out that the total maternal conditioning—emotional climate if you will—with the child produces disturbance in function or basic security and not simply the conditioning in the bowel zone There are mothers and some of these are present in the series that I mentioned who handled the child in such a way as to bring about emotional deprivation in the oral stage when the child was being weaned or fed orally but who on the surface had handled the bowel training period in a very permissive way One cannot generalize in such a gross way and say that this factor is always present

DOCTOR PRUGH I should like to make one statement which grew out of the remarks that were made which I think is worth saying and that is the fact that parents today are under a bombardment of pronouncements by experts from all quarters They develop expertitis in a sense and I think the temptation is on all our parts to recognize the emotional component in a problem and then impute a certain amount of blame to the parent for not handling the situation with what we regard at this particular moment in this particular social setting as a more constructive technique I think this gives me an opportunity to point out what Dr Moses and others have mentioned *i e* the dichotomy or the opposite character of conscious and unconscious feelings Most of the mothers that I have seen of children that have problems do not consciously reject their children They consciously wish to give their children emotional security They would like to do things in a constructive way but unconsciously there may be hostility toward the child perhaps strong needs for cleanliness and it is this conflict which produces the problem for the parent One has to move very slowly with the parents and avoid the temptation to point out to them the exact nature of the problem because they are not ready for insight of that kind At one moment in the case the parent is ready then one works along with the child

CHAIRMAN HOLLANDER Dr Grimson in connection with your demonstration of the distended bowel loops in megacolon I wonder if you knew of any data on the pressures which are attained within them

DOCTOR GRIMSON No but they are enormous They are impacted If you put your hand on there there is no method to get a balloon up and measure it The prerequisite would be to evacuate it which we can often achieve We have not used the balloon studies but the same problem relates to the esophagus With adequate drainage the esophagus or the megacolon will *become normal in size and apparently normal in function without any surgery*

May I answer Dr Winkelstein? I believe in medicine and in surgery and Dr Winkelstein has given me a chance to reassert my beliefs I do say that the extrinsic sympathetic and parasympathetic in the normal individual are secondary means Certainly I do not deny that Some of the stresses we see were not parasympathetic or sympathetic They were total reactions of the body I still believe the sympathetic and parasympathetic play a minor role

and in the instances in which we have done colectomy shortening the colon there may be a length of bowel that just does not work It lies there day after day with gas in it Medicines at the best, don't affect it We have not tried psychotherapy I have not been too encouraged The ulcerative colitis I see now is just as bad an ulcerative colitis as that which came to surgery ten years ago There are important factors in the etiology For practical therapy, I think we are dealing sometimes with an intrinsic pathology What I mean to say is in these large colons some place along the line distal or in the dilated or maybe the whole colon perhaps there was something wrong not in the central connections nor in the central connecting pathways but directly in the intrinsic plexus itself I wish we had sectioned them to get the evidence but the likelihood seems very strong

Doctor Grace Doctor Moses asked if some of the patients were schizoid or schizophrenics I think that is a difficult question to answer, and depends on what kind of patients are referred to the psychoanalyst or psychiatrist, and whether they would get a higher percentage of patients that are schizoids or with schizoid tendencies than I should get

I have a series of about 40 people now I have only one schizoid that I know Whether these people have been seen by consultant psychiatrists I am not sure

Doctor Moses Will you say how sick are the other patients from the general psychiatric point of view?

Doctor Grace I don t know what you mean In what terms are you measuring?

Doctor Moses Psychoneurotic state mild moderate, severe

Doctor Grace Moderate and severe Doctor Moses also suggested that we utilize more the techniques of psychoanalysis in obtaining information and data about the patients and it is well for all of us in this conference to be aware that there are no data to support the contention and the feeling that such techniques are better than any other data being used at the present moment

Doctor Code I have a question that I should like to direct to Doctor Grace and Doctor Almy I am tremendously impressed by the observations that Doctor Grace and the group made at the bedside of changes in the bowel and bowel function but I am confused when confronted with the grouping of the types of reaction that occur in the individual when this does occur In the group of reactions that he mentioned there were anger resentment diarrhea increased motor function and the like that might together be called caught in a trap ' diseases as was mentioned earlier Is there a conflict between his concept and that of Doctor Almy?

Doctor Almy I wonder how much we can learn from this kind of study because many of us have had great difficulty in reaching agreement on exactly how to describe certain qualities of emotional tension The only kind of psychosomatic study which has seemed to me to be unimpeachable is that in which certain bodily changes have been related to the phenomena of emotional tension For example we have accepted the fact for years that when a lady blushes she is probably feeling a certain emotion We have accepted as fact

that tears are not only expressive of emotion but of a certain quality of emotion Certain phenomena in the gut happen when people blush and certain other phenomena happen when they weep Up to that point I think that I am on safe ground in reading something into the emotional reaction of the patient Beyond that I am afraid that not even psychiatric lingo can help me very much I really think that in order to progress further with this kind of re search or to even approach the quality of investigation which Doctor Moses suggests we are going to have to rewrite the rule book for clinical investigation

CHAIRMAN HOLLANDER Does this mean Doctor Almy if we could devise an adequate language for describing or cataloguing various emotional reactions that we might hope to establish a one to-one relationship between such emo tional categories on one hand and physiological manifestations in the bowel on the other?

DOCTOR ALMY I think it would take more than language I think it would take objective indications upon which we can all agree whether they are in the realm of other autonomic responses like blushing or weeping or whether they are in certain characteristic phrases or turns of the head and the like If we can agree that certain phenomena are indicative of a certain quality of emotional tension then we can proceed to relate those phenomena to other bodily functions which are under study

CHAIRMAN HOLLANDER It does not necessarily mean that there is an in variant causal relation between them That is an open question

DOCTOR ALMY That is for us to find out

DOCTOR KEMPF May I comment on this? I have been working on this for 40 years I have probably done more work on it than anybody else in the world You have this problem What does the situation mean to the patient not what the situation means to you? But what does it mean to the patient? A certain kind of situation will mean one thing to one patient and to another patient who seems to be in a similar situation it will have quite a different meaning One patient will have a colitis as a reaction Another fellow may have a gastric ulcer as a reaction The meaning is entirely different Another one may have vascular hypertension from what seems to be a similar situation Still another one may have a cardiac spasm as the result Now the important part of the clinician is to tie up with the psychopathologist and learn how to discriminate the meaning of the situation the family situation the emotional situation for the patient So far if you read all of these books on the study of colon and stomachs there has always been generalized a picture of fear hate hate fear and so on—all kinds of clinical pictures as if you are expecting the weak organ to break down in the fear hate situation I don t think that is fair or good science It is not good logic We have to get the conditioning experience and what the situation means to the individual Then I think we will get to the bed rock of this thing

DOCTOR JORDAN Having for years observed the effect of disease upon the mind I should like to call attention to the fact that we must not forget that aspect in other words the somatic aspect of the whole problem Let us put forth the hypothesis that the young person the young student in college gets ulcerative colitis that he has no background of psychogenic trauma or any

thing abnormal psychic He gets the disease What effect does that have upon his mind? Many of these qualities which these patients are supposed to have, despondency, *etc*, might easily be the result of a disease rather than the cause of it I don't think we should forget that aspect of this whole problem

DOCTOR GRACE The problem that Doctor Code raises is the problem of why does one person get one disease and another one get another in presumably the same situation This is the biggest stumbling block that anybody in this kind of work is faced with, whether using the techniques we practice or some other similar ones There are those more facile in wrangling over the words 'fear anger, hate It does not mean anything more You can get a real experience if you go to the dictionary and see how the different words are defined We have been approaching this problem in a way which intends to omit words that describe emotions as part of the syndromes in using the question of what the patient wants to do about the circumstances One of the reasons for this is there are so few words in the English language that can be utilized to describe the feeling state With such a technique used to define specificity of reactions we think there is at least some light toward the way in which one may go further The difficulty between Doctor Almy and myself is not one in collecting data or observations It is a difficulty in interpreting what we see

DOCTOR GRIMSON I seem to be in the extreme minority, but I have a very strong recollection that some of the things that are being spoken of here in the way of stress and anger and ways of people getting angry are not much unlike in behavior, as far as physiology is concerned to conditions that Cannon and others describe as sham rage Sham rage produces a lot of changes in the animal Probably in the patient we are beginning to see signs of what sham rage does Is that necessarily saying what the etiology of hypertension is what the etiology of ulcer is? Why do you ask the question? Why does one man who is nervous—I am nervous we are all nervous—get ulcer one man get gastric ulcer another man ulcerative colitis? I don t manage to have anything I may have a heart condition What is the etiology of this and what role does ulcerative colitis play? How may ulcerative colitis be influenced by this? What is the etiology of hypertension ulcer coronary arteriosclerosis, and other factors? In what way does the mechanism by which this disease differs and progresses cause the patient s nervousness and then cause this? Conversely, how does it cause the reverse? Certainly I am in favor of blocking the parasympathetic and the sympathetic I have done so many times I believe in the psychosomatic methods Here we have the cart before the horse and that is the question you indicated a minute ago Doctor Hollander

CHAIRMAN HOLLANDER It seems to me that Doctor Grimson and others have struck at the heart of the problem the choice of organ, and the possibility that there may be certain specific personality structures associated with the specific disease pictures I think we are recognizing today that this is not the case It is a wish in a sense that we could find specific personality structures with specific disease entities or specific emotions which will produce specific effects It seems to me that there are two basic factors to use an analogy with an immunologist one might say the strength of noxious stimulus and the

strength of the host, the resistance of the host It is the interaction between the two and the conflicts set up in the individual s mind which produce the need for the use of adaptive mechanisms which seem to be brought about by certain biological conditions biological equipment psychic conditioning and confluence of other factors never by any single cause Just to use one technical term I should like to use the word ego and to define it in a way that a previous instructor of mine used which I think is a rather graphic pertinent one This instructor, discussing the alcoholic personality with immaturity and a tendency to use alcohol in attempted adaptation though unhealthy and in defining the ego which is admittedly a slippery term said Ego is that portion of the personality which is soluble in alcohol In other words the ego does dissolve in the face of stress and I think it is the quantity of stress from the outside or intensified inner conflict which produces the weakness of the ego if you will and it is the strength of the personality the host the resistance of the host that is brought to the situation which determines whether a particular set of conflicting forces will be pathologic or not I do not think it is just the emotion of fear or the emotion of anger since we all have these as pointed out but the degree of conflict aroused the strength of the personality to deal with it and the types of defenses, if you will adaptive mechanisms which are available that in this multiple fashion do determine the symptomatology I think this is all we know at this point and it is very little

Doctor Moses May I make one comment? Just to answer, I don t see why at this stage of science there should be a conflict between psychology and the psychoanalytic techniques Doctor Grace If you accept the validity of one you must accept the general validity of the other It is an extension a more intensive technique of Doctor Grace s psychological factors All one does in analysis is do it more intensively over a longer period of time To date this is in psychosomatic disorders at most an experimental technique Because of that it is justifiable to try these techniques and see how they actually work

There was one other point I wanted to make Whenever somebody tries to get another person to quantitate psychosomatic factors difficult as that may be whether psychoanalyst or internists immediately everyone jumps to the conclusion that that means 100 per cent psychogenicity 100 per cent 1 1 correlation It does not mean anything of the sort Perhaps in some disorders just like weeping it may be 100 per cent psychogenicity The probability is this will vary in various conditions and the only way to find out is to study these questions It is quite possible that in a condition like essential hypertension that we are definitely dealing with some of the definitely genetically determined autonomic patterns of reactivity which possibly with emotional patterns of reaction constitute the clinical condition Possibly the same thing may be found in colonic disease Possibly it may not be found The only way we can actually find out is to study these conditions with the most intensive techniques that we have available Psychoanalytic psychologic techniques are valid scientific techniques today

In a sense from a general point of view the data can be repetitious can be observed by many observers Possibly on the finer details there may be

disagreement, as there is about other investigative techniques, but the general findings of psychological and psychoanalytic techniques are scientifically established and as such unless there is some practical handicap against using them they should begin to be used This however, does not invalidate the excellent psychological studies that Doctor Grace has made I think there is room enough in these various conditions for all of these techniques

Doctor Alfred P Ingegno I should like to know whether in Doctor Grace s experiments there was any attempt at dietary control, particularly with respect to the possibilities of allergic reactions to food

Doctor Grace The experiments were short termed lasting only a few minutes

Doctor Ingegno I mean during the period of time that these studies were made

Doctor Grace We did not keep the food diary at any time on any of these people

Part III Pharmacology of the Abnormal Colon

INTRODUCTORY REMARKS TO PHARMACOLOGY OF THE ABNORMAL COLON

By McKeen Cattell

Cornell University Medical College New York N Y

We have already heard a series of papers dealing with the subject of the normal physiology and pharmacology of the colon followed now by a series of communications grouped under the title of the Pharmacology of the Abnormal Colon Probably we shall find little difference in the fundamental pharmacology of the abnormal colon in comparison with the normal colon There are a number of practical considerations however which have a bearing on the management of functional disorders of the gastrointestinal tract which determine the choice of drug therapy

One interesting and rather puzzling fact might be mentioned Clinically it is known that atropine is fairly effective in suppressing spasmodic contractings of the gastrointestinal tract whereas it has comparatively little effect on normal motility In the cat it is a well known experimental fact which we have our students demonstrate for themselves every year atropine is peculiarly effective in suppressing the response of the gastrointestinal tract to injected acetylcholine whereas it has very little effect on the response produced by stimulation of the vagus nerve That would lead one to conclude if it were possible to transfer the results from the animal to man that atropine would not be particularly effective in spasm arising from activity mediated through the central nervous system I question whether that is the actual experience of the clinicians Perhaps we may have some discussion of the point If the abnormal colon responds to drugs in a peculiar fashion it is hoped that will become apparent during the present series of papers Perhaps Doctor Travell will be able to tell us the circumstances when the stimulant laxatives are most effective and Doctors Tainter and Buchanan when to use bulk laxatives Then if they do not have the answers we hope we may learn from the contributions of Doctors Seed and Harris and Doctors Cass and Frederik how we may proceed with clinical comparisons in order to obtain them To what degree antispasmodics are effective in the hyperactive colon we hope to learn from Doctor Ingegno and finally from Doctor Gray whether or not fecal lysozyme activity has any bearing on the problem

disagreement, as there is about other investigative techniques, but the general findings of psychological and psychoanalytic techniques are scientifically established and as such unless there is some practical handicap against using them they should begin to be used This, however, does not invalidate the excellent psychological studies that Doctor Grace has made I think there is room enough in these various conditions for all of these techniques

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referring to such a drug as neostigmine, one would say that it ' stimulates intestinal motility or "produces diarrhea not that it causes catharsis

The implications of the term irritant are not wholly valid as applied to the assortment of stimulant laxatives which I have listed By definition an irritant drug elicits signs of local inflammation redness swelling and in the case of the gut increased secretion of mucus[3] But powdered phenolphthalein may be instilled into the conjunctival sac without ill effect and if placed in intestinal loops it fails to cause evidences of local irritation even when peristalsis results[4] Loewe[1, 5, 6] has suggested that the cathartic action of phenolphthalein in man and the rhesus monkey may depend on the affinity of certain linkages in the phthalein molecule for amino groups of the tissues since he found that imide affinity parallels laxative potency Hubacher *et al*[7] have pointed out that exceptions have been found to any law so far proposed regarding the relationship between chemical structure and laxative activity of the phthaleins Loewe[1] himself states that the above hypothesis is far from being proved but [it] draws attention to the possibility that a specific reaction between the drug and some body component may be the basis of the mechanism of action

Thus it seems that increased propulsive motility caused by a local stimulant action of the drug on the gut may be differentiated from motility initiated reflexly by local irritation Possibly the term chemical would be more appropriate than irritant or stimulant in classifying the mechanism of action of this group of cathartics

It is nevertheless true that most of the cathartics generally included in this category are capable of producing local irritation under the conditions which ordinarily obtain in the intestinal tract Such irritation as occurs is usually mild and the increased fluid content of the resulting stool is probably attributable to the accelerated passage of fecal matter through the descending colon with insufficient time for reabsorption of water from this site In the case of the hydragogue purgatives however copious effusion of fluid into the intestinal tract, caused by marked local irritation is also a factor

Local irritation of the stomach that results in nausea and vomiting is obviously an undesirable side action of a cathartic The therapeutic usefulness of this group of materials depends partly on the fact that the irritant cathartic principle as a rule is not liberated from the crude drug until it has left the stomach and therefore vomiting is not induced For example ionized mercury is slowly released from insoluble mercurous chloride at an alkaline pH Emodin is slowly hydrolysed from the glycosides in cascara senna aloe, and rhubarb Castor oil is a bland neutral fat until it is hydrolyzed to ricinoleic acid in the small intestine It is sometimes forgotten that bile is necessary for the digestion of this fixed oil and that in the presence of biliary obstruction castor oil given as prep for X ray examination of the abdomen may fail to empty the bowel Phenolphthalein also requires the presence of bile in the intestinal tract to produce catharsis[8] This does not apply to the anthraquinone cathartics or calomel[9]

This need for bile in the intestine is quite apart from the question as to whether the stimulant cathartics act as choleretics or cholagogues The con

PHARMACOLOGY OF STIMULANT LAXATIVES

By Janet Travell

Department of Pharmacology Cornell University Medical College New York N Y

I have been asked to contribute this paper, not because of any extensive investigations of cathartic drugs, but because of our interest in rational therapeutics expressed in our Cornell Conferences on Therapy[1] which dealt with the rational use of cathartic agents

At the conference on which this monograph is based, emphasis was placed on the need of the abnormal colon for rest in general and in particular for relief from irritation by cathartics With respect to chronic constipation, or functional bowel stasis such rest is admittedly desirable Presently, however I shall quote some figures on the amounts of stimulant laxatives actually prescribed which suggest that ideal therapy of this condition is not always attained In view of their widespread use, salient points in the pharmacology of these drugs merit review especially since, in recent years, the stimulant laxatives have received less attention than the bulk laxatives

The scope of this paper does not permit discussion of the place of stimulant cathartics in chronic constipation In acute constipation, however, it is clear that legitimate indications often do exist for giving these preparations, for instance during administration of constipating drugs such as codeine, morphine and ephedrine, during bedrest and hospitalization, after dietary indiscretions, and after certain vermifuges Also preparation of the patient for roentgen examination of the abdomen usually includes catharsis by one of this group

The stimulant cathartics comprise several widely different types of compounds mainly of vegetable origin (1) anthraquinone derivatives contained in cascara sagrada aloe senna and rhubarb (2) phenolphthalein and other phthaleins and coal tar dyes[2] (3) ricinoleic acid liberated from castor oil (4) the hydragogue "drastics ' potent resins and alkaloids of podophyllum, jalap colocynth elaterin, gamboge, and croton oil (5) sulfur, and (6) calomel

Mode of action The "stimulant "or ' irritant cathartics as they have been termed, are to be contrasted with the mechanical ' laxatives the gums, salines liquid petrolatum and water which promote peristalsis mainly by increasing the bulk or altering the consistency of the stool

These cathartics are also to be distinguished from systemic agents which stimulate intestinal motility only after absorption into the blood stream for example picrotoxin vasopressin and the cholinergic drugs Unlike the latter, the irritant cathartics are believed to act only when they are present within the lumen of the intestinal tract This action occurs even when evacuation is induced by their parenteral administration For instance emodin (trihydroxymethyl anthraquinone) causes catharsis when injected intravenously The effect is thought to depend on the excretion of the drug into the colon In fact by common usage the terms laxative cathartic and purgative' always imply a local site of action within the gut On the other hand in

fluid into the gut. Hydrophilic or hygroscopic agents retain water by preventing its reabsorption from the colon

Intensity of action is judged by the number of stools their consistency and water content Changes in the character of the stool may be determined directly in normal subjects or the number of positive responses in constipated subjects may be used as an index of effectiveness It is generally assumed that the normal and constipated colon behave similarly in these respects The inflamed colon however is unquestionably more sensitive to irritant cathartics than is the normal

It seems likely that any potent drug in this class may have either a laxative or purgative effect according to the dose given Thus in China a teaspoonful of castor oil has been included in the daily diet to produce a mild laxative effect whereas in this country 60 cc are commonly given to produce vigorous purgation The general notion that a given drug possesses only one of these effects stems from the size of its traditional dose Thus cascara in customary dosage is regarded as a mild laxative suitable for daily use in chronic constipation If the dose is sufficiently increased however or the standard dose is taken by a highly susceptible person purgation results Gold[1] has made a plea for 'greater attention to the adjustment of the dose to the need of the individual case He says The problem here is the same as that with so many other drugs we spend more time shifting from one preparation to another than we do solving a more basic problem determining the needs for the individual case '

Tolerance As far as I know the development of tolerance to stimulant cathartics has not been investigated in a systematic manner Tolerance is often thought to be in evidence in the patient with chronic constipation who constantly shifts from cathartic to cathartic because no one preparation is effective for any length of time The ease of adjustment of the bowel to new stimuli is well known and it is possible that the diminishing effectiveness of a given cathartic is attributable to the wearing off of a placebo effect rather than to tolerance

Habituation to cascara is said to occur seldom even after long use One wonders whether in this situation the need for the cathartic may not have passed and whether a placebo at this time might not suffice equally well Application of the double blindfold method to the investigation of tolerance to these cathartics should prove fruitful

Cumulation The capacity of the body to store mercury is well known and calomel on repeated administration may give rise to cumulation of this metal

Phenolphthalein as I have indicated undergoes a continuous absorption re excretion cycle As it is absorbed from the intestine part of it is excreted in the bile and this portion is then subjected to reabsorption Gradually the material is eliminated from the body by way of the colon and the kidneys The feces probably contain both absorbed and unabsorbed fractions Under these circumstances cumulation of phenolphthalein takes place over a period of a few days but on a fixed dosage the process is self limiting

Use and Preparations *Hydragogue purgatives* have fallen into disrepute because very small doses may produce excessive purgation accompanied by gastroenteritis and circulatory collapse One drop of croton oil may cause

sensus is that they do not stimulate the liver cells to secrete bile nor the gall bladder to empty its contents

Site of action With certain exceptions the stimulant cathartics cause evacuation by an action directly on the small intestine and indirectly on the colon The coordinating reflexes of the intact gut are such that increased motility of the small intestine is followed almost at once by increased motility of the large intestine and vice versa Even when the connection between the small and large intestine is severed catharsis may follow promptly after oral administration of a cathartic For example, this has been shown to be true for the saline, magnesium sulfate [10] which is relatively nonabsorbable and in any event, does not stimulate intestinal motility when injected into the blood stream Under these circumstances the evacuation induced must depend on coordinating reflexes initiated in the small intestine Thus all laxatives which stimulate peristalsis in the upper bowel tend to empty the colon

Phenolphthalein and the anthraquinones in therapeutic doses do not act directly on the small intestine In the intact gastrointestinal tract, increased propulsive activity of the colon is not observed until several hours after ingestion when the material has arrived in the colon The specific action of cascara on the large bowel was also demonstrated by Grabfield[11] in perfusion experiments on loops of intact gut in rats using a 1 10 000 solution of fluidextract of cascara When a loop of the small intestine was perfused there was no effect on motility but similar perfusion of the large intestine stimulated motility first of the large and after a short interval of the small intestine also This experiment demonstrates not only the site of action of cascara but also the corrdinating reflexes which link the different portions of the gut At this symposium Doctor Sara M Jordan spoke appropriately of the unity of the gastrointestinal tract

The selective site of action of cascara senna rhubarb and aloe on the colon makes these drugs well suited to administration at bedtime to obtain evacuation the following morning In customary dosage they usually act in about eight to ten hours after ingestion Slow release of the emodin principles from the glycosides in the crude drug during transit to the colon has been thought responsible for the lapse of several hours before evacuation occurs The colon is about 1000 times as sensitive to the action of emodin as is the small intestine [12] Actually defecation has been shown to take place in the cat after oral administration of senna when the small and large bowel are surgically disconnected [1] The delay therefore must depend on the time sequences of the cycle of glycoside degradation to anthraquinones and their absorption from the gut and re excretion into the colon Phenolphthalein likewise has a selective action on the colon but may act sooner (four to eight hours) than these anthraquinone cathartics This difference is probably attributable to a more rapid absorption re-excretion cycle

Intensity of action The cathartic action of a drug depends fundamentally on its net effect on the propulsive motility of the colon A laxative drug has been defined as one which produces a formed stool a purgative' a semi fluid (or semisolid) stool and a drastic a watery evacuation accompanied by local irritation [9] A hydragogue is any cathartic which causes effusion of

siderably larger than those which obtain for the various pharmaceutical preparations laxative and otherwise in which glycyrrhiza is incorporated as a flavoring and diluent Nevertheless, because of marked variations in the dose of licorice required by different individuals to produce clinical effects one is entitled to wonder how often the repeated use of compound powder of senna contributes to the appearance of signs of congestive heart failure when it is taken regularly by the elderly

Curiously U S P XIV which admits no senna preparations describes 5 preparations of licorice the crude drug the extract pure extract fluidextract and syrup without any assay of potency or even specific directions for making the extract For only one preparation the fluidextract of glycyrrhiza is a dose stated namely 2 cc, the therapeutic indication is probably its old use as a demulcent for the irritated pharynx

Aloe (*aloes*) and aloin which is a mixture of the active principles derived from aloe are included in U S P XIV The U S P dose of aloe is 0 25 gm For aloin a chemical assay of emodin is directed and the U S P dose is 15 mgm Textbooks state that aloin causes pelvic congestion and may lead to abortion but this assertion has been questioned [19] The widest use of aloe is in patent medicine cathartic pills in which it is often combined with an antispasmodic to prevent griping The nice tasting chocolate covered ABS pill (aloe bella donna and strychnine) occasionally holds the limelight not because of its cathartic effect but for causing accidental strychnine poisoning in children Strychnine has no rational basis for inclusion in this combination

Cascara sagrada in the average U S P dose is a mild cathartic which rarely causes griping or watery evacuations McGuigan *et al* [20] have shown however that the U S P dose of cascara (2 cc of the aromatic fluidextract) in normal and constipated subjects is only about one half as effective as the U S P dose of magnesium sulfate (15 gm) Much larger amounts than the U S P dose of cascara may be required to produce satisfactory evacuation the dose of the aromatic fluidextract may be as high as 12 cc in some adults [21] Thus if the U S P dose does not produce laxation it should be increased until the desired effect is obtained

Preparations of cascara sagrada listed in U S P XIV include the extract fluidextract and aromatic fluidextract In making these preparations the amount of the crude bark which is used to prepare 1 gm (or 1 cc) is 3 gm for the extract and 1 gm for both the fluidextract and aromatic fluidextract The official dose of the aromatic fluidextract is twice that of the plain fluidextract because approximately one half of the active cathartic principles is thought to be destroyed in the process of preparing the aromatic fluidextract owing to pro tracted boiling with water This procedure also removes some bitter sub stances and together with the addition of volatile oils and licorice for flavor ing it improves the palatability of the preparation The aromatic fluidextract contains 4 per cent of glycyrrhiza extract The alcohol content of the two fluidextracts is the same about 18 per cent

The U S P XIV dose of the extract given as equivalent to 2 cc of the arom atic fluidextract is 0 3 gm (1 tablet) In tolerant individuals in whom the effective dose is 12 cc (2½ teaspoonfuls) of aromatic fluidextract 6 such tab

vomiting and extensive fluid evacuations accompanied by abdominal pain and tenesmus 20 drops have proved fatal[9] None of this group is official in the U S P XIV

Calomel likewise has no place in therapeutics as a cathartic, since the danger of mercury poisoning is ever present, especially following repeated doses or in the presence of intestial obstruction when the expulsion of the unionized salt from the intestinal tract is delayed Mercurous chloride was deleted from the U S P XIV

Sulfur is sometimes given to children in the form of the spring tonic, "sulfur and molasses" This empirical use may have a basis in the reported effectiv ness of sulfur as a vermifuge for pinworm[13] Sulfur has gone out of fashion as a laxative probably because the hydrogen sulfide formed in the intestinal tract which is though to act as a mild irritant, imparts a disagreeable odor to the stools and even to the breath Sulfur is also said to provide bulk and to soften the stool[12] The U S P XIV dose of precipitated sulfur is 4 0 gms Sulfur constitutes 8 per cent of compound powder of senna

Rhubarb contains glycosides which liberate at least three cathartic anthra quinones emodin chrysophanic acid and rhein (no cathartic principle is present in the rhubarb grown in the United States as an article of diet) Rhu barb also contains a considerable quantity of tannin which tends to produce the opposite effect that is, constipation In fact, small doses of rhubarb are recommended for the treatment of diarrhea[9] This preparation is not a satis factory cathartic, and its high content of oxalic acid also tends to limit its use Several preparations of rhubarb were included in U S P XIII but none was admitted to U S P XIV

Senna like rhubarb has fallen by the wayside or so one would conclude from reading the literature Senna and its preparations have been deleted from U S P XIV However compound powder of senna better known by its old synonym, compound licorice powder is still widely used by many people (some of whom used to take liquid petrolatum) and is sometimes recommended as an alternative to castor oil for prep' prior to X ray examination of the abdomen The U S P XIII laxative dose of compound licorice powder is 4 0 gm (0 5 gm of senna) but for X ray preparation the dose is usually 16 0 gm (2 0 gm of senna) Textbooks state that senna may cause griping but this is certainly not a universal side action Probably a more important drawback is its high content of licorice which constitutes about 25 per cent of compound powder of senna by weight

Licorice is subject to two misconceptions (1) that it is a cathartic and (2) that it is an inert pharmacologic material Glycyrrhiza has been shown to pos sess an action similar to that of desoxycorticosterone acetate (DOCA)[14, 15, 16, 17, 18] In normal subjects, fairly large amounts of licorice cause a gain in body weight owing to sodium and water retention and under suitable conditions may substitute for DOCA in Addison s disease The constituent of the crude drug responsible for this action in glycyrrhetinic acid a polyterpene which resembles in its structural formula the steroid group to which DOCA be longs[15, 16] The doses of the glycyrrhiza preparation which produce corti costeroid effects range from about 15 to 45 gms daily and are therefore con

TABLE 1

PURCHASE OF LAXATIVES BY DEPARTMENT OF PHARMACY NEW YORK HOSPITAL 1952

Drug	Amount purchased	Average dose	Calculated total No. doses
Cascara sagrada extract	50 000 tablets	0 3 gm	50 000
Aromatic fluidextract of cascara sagrada	36 gals (316 lbs)	2 cc	72 000
Compound powder of senna	50 lbs	4 gm	5 625
Castor oil	48 gals (400 lbs)	30 cc	6 360
Liquid petrolatum (mineral oil)	648 gals (5 200 lbs)	30 cc	86 184
Magnesia magma (milk of magnesia)	552 gals (4 600 lbs)	15 cc	184 000
Magnesium citrate	208 gals	300 cc	2 773

One gallon = 4000

vermifuge since it reduces the toxicity of the host to this agent which otherwise has a narrow margin of safety

Usage TABLE 1* shows the purchase of laxatives exclusive of the gums made by the New York Hospital Pharmacy in 1952 The figures may be assumed to parallel the amounts prescribed because the inventory carried over by the pharmacy from one year to the next is very small The hospital has about 1200 beds and the distribution of the drugs listed includes those also issued through the Outpatient Department which handles about 250 000 visits per year

(1) Leading the list is *magnesia magna* (milk of magnesia) with nearly 200 000 doses calculated on the basis of three teaspoonfuls to a dose Based on the quantities purchased its use was approximately 552 gallons or 4600 pounds *Magnesium citrate* was used in the amount of 208 gallons or 2773 doses Less than 100 doses of any other saline were issued

(2) *Cascara* is next in order the number of calculated doses being 122 000 Aromatic fluidextract of cascara sagrada accounted for 72 000 doses and cascara tablets for 50 000 doses

(3) The other anthraquinone preparation in general use is *compound powder of senna* Approximately 50 pounds were bought accounting for 5625 doses (4 gm each) Together the cascara and senna preparations amounted to about 400 pounds or one fifth of a ton

(4) *Liquid petrolatum* (mineral oil) was used in almost astronomical figures—a total of 648 gallons or 2½ tons This accounted for 86 184 doses of 30 cc each

(5) *Castor oil* was not a laggard 48 gallons or 400 pounds were used which provided 6 360 doses of 30 cc each Nearly 3 tons of liquid petrolatum and castor oil were used

(6) *Phenolphthalein* is not included in the New York Hospital Formulary One pound was purchased by the Pharmacy in 1945 and this amount is still being used as needed in the form of a reinforced emulsion of liquid petrolatum [31]

In view of their widespread use I should like to close by emphasizing some

Figures submitted by M N rma N B k Apothecary Chief New York Hospital Pharmacy

lets would have to be taken. Most patients would object to so many pills but not to a couple of teaspoonfuls.

Cascara sagrada in suitable dosage is probably the most satisfactory of the stimulant cathartics for regular use over long periods of time. It produces a minimum of disagreeable side actions, and toxicity is rarely even mentioned in textbooks of pharmacology. It should be noted that the emodin principles are excreted in milk and that a nursing infant may develop diarrhea as a result of the mother's taking cascara.

Phenolphthalein, as described in U.S.P. XIV, is *white* phenolphthalein and the U.S.P. dose is 60 mgm. Unofficial yellow phenolphthalein is a mixture of phthaleins and is 2.5 to 3 times more potent in its laxative effects for the rhesus monkey than is the official preparation.[5, 23, 24] Assays have shown that no one of the components of yellow phenolphthalein is more active than phenolphthalein itself[23] and its greater laxative potency may be due to differences in physico-chemical state, such as water repellency.[24, 25] One major difficulty in the way of investigation of the potency of the phthaleins is the enormous interspecies and interindividual variation in susceptibility to these compounds. The rhesus monkey is the only species known to give quantitative responses similar to the human.[1, 7, 26]

Clinical studies show that, as in the case of the aromatic fluidextract of cascara sagrada, the single U.S.P. dose of phenolphthalein is, on the average, only one half as effective as the U.S.P. dose of magnesium sulfate.[9] Owing to cumulation, however, the laxative action of a dose of phenolphthalein may last for two or three days. This prolonged action is followed by a period of secondary constipation which tempts the patient to take another dose and so tends to establish a cathartic habit.

Other disadvantages in its use include allergic dermatitis and excessive purgation. Beckman[21] notes this common fault of phenolphthalein: "A small dose sometimes acts excessively, while a large dose may fail to act at all."

In view of the enormous number of patent medicines containing phenolphthalein which are consumed annually by the constipated public in the United States and because of the minimum of serious toxic effects reported, we may conclude that phenolphthalein is a relatively safe material in the dosage employed. In fact, the ingestion of large doses accidentally by a few children, even 100 times the therapeutic dose, did not cause serious poisoning.[27] Phenolphthalein is excreted in the urine in free and conjugated form, but the evidence that it causes damage to the kidney is unsubstantial.[9] There is also no evidence that it causes liver damage even in jaundiced patients.[29]

Castor oil is a useful cathartic in acute constipation and for preparation of the patient for X-ray examination of the abdomen because it produces relatively complete emptying of the bowel. The U.S.P. XIV dose is 15 cc, although two to four times this amount is usually given to adults.

Precautions should to taken to rule out inflammatory conditions of the intestinal tract, such as acute appendicitis or ulcerative colitis, or an early pregnancy,[30] before administering this, or, in fact, any other cathartic.[1]

Castor oil should always be given when oil of chenopodium is used as a

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general contraindications to the use of stimulant cathartics (1) pregnancy, (2) menstruation, (3) lactation, (4) intestinal obstruction, (5) abdominal pain, (6) acute diarrhea (trichinosis excepted) (7) general debility (danger of excessive purgation)

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It is felt that these conditions were sufficiently double blind to prevent any bias on the part of the experimenter or patient from influencing the results For the protection of the patients a second physician was available who knew the code In the event that any problems occurred related to laxative therapy which required knowledge of the code for adequate judgment this physician could be called upon for advice

The second basic principle of good design is the randomized sequence of administration The underlying thought behind randomization is to distribute evenly over all the medications all the variability in the experimental situation except that owing to treatment Any systematic errors are thus eliminated For instance in a previous study on laxatives[6] it was shown that if a subject has a marked laxative effect from a medication on one occasion he is apt to have an increased laxative effect from a subsequent medication on a psychological basis The subsequent medication was given a week later when all pharmacological and physiological effects of the first medication had completely disappeared Obviously if a mild laxative always follows a strong laxative it will falsely appear to produce a stronger laxative effect If all medications follow a strong medication with equal frequency then the psychological effect of a strong medication will be evenly distributed over all treatments and any apparent differences between treatments are more apt to represent true differences due to the medication

Another source of variation in a laxative study is diet Some diets exert a laxative effect and some a constipating one If all subjects received the same diet every day and at the same time received the same medication obviously one would be unable to distinguish whether or not any effect observed was owing to diet or to medication By randomizing the order of administration the number of patients receiving any particular medication on a given day will be about the same Hence variability due to diet will be evenly distributed

In the examples to be shown randomization has been achieved by the use of a series of Latin squares (TABLE 1) TABLE 2 shows one of the code cards used Patient names are entered on the card according to their room numbers The card then gives the sequence in which each patient is to receive his medication Each block of six patients constitutes a complete Latin square *i e* all six medications are given to each patient in the course of six weeks On any one day each of the medications is being given to one of the six patients and the order both per day and per patient is randomized The code was changed after three weeks hence the sequence for the last three weeks is marked with an 'X' to prevent the nurse from accidentally remembering part of the code and thereby correlating the code letters for the last three weeks with those of the first three

With these principles in mind the next problem is what questions about laxatives are we trying to answer and what measures should be used to answer the questions? In the cases illustrated below the problem was to find a method of comparing laxatives We did not want to compare all possible effects of laxatives or to study basic mechanisms A simple measure which was related to intensity or type of laxative effect was desired

By definition a laxative is a medication having the ability (1) to soften the

SOME FACTORS IN THE DESIGN OF APERIENT STUDIES

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Subjective verbal reports or simple performance tests provide the simplest and easiest means of clinically evaluating the effectiveness of most forms of therapy Indeed this is the method used by physicians every time they see a patient They ask a patient how he feels how his headache or backache is or how well he can walk or climb stairs *etc*, depending on the situation By the use of proper design in the administration of medication and recording results such simple information can be quantitated with a fairly high degree of accuracy and provide a reliable index of the effectiveness of treatment The inherent difficulty in using subjective verbal reports of symptoms or simple performance tests is the very considerable influence exerted by interest on the part of the experimenter and on the part of the patient By proper design this interest effect may be differentiated from the results of drug therapy

The basic principles for evaluating therapy on the basis of simple verbal reports or performance tests are well known They are primarily two in number (1) neither the subject nor the experimenter should know the exact nature of the medication and (2) the order in which the medication is given should be randomized These principles have been very successfully applied to the evaluation of drugs in a number of fields[1,2,3,4,5] However some investigators still prefer to obtain so-called objective data *e g* sedimentation rate blood pressure serum lipoprotein levels *etc* in the belief that there is then no need for these two basic design principles Often such investigators go to considerable trouble doing elaborate and expensive tests in order to obtain objective data' and thus eliminate any subjective influence on their results when a simple subjective report would supply all the information needed As time goes on it is becoming more and more apparent that no matter what criteria of effectiveness are used the results will be unreliable unless one adheres to these two basic design principles

The first of these two principles neither the subject nor the experimenter should know the exact nature of the medication has been termed, for short the principle of the double blind study[5] The studies we have done have been 'double blind in that the patients have known only that they were receiving a laxative They have not known the nature of the laxative whether it was a saline stimulant or bulk laxative or when it was changed All medications have had an identical appearance flavor and taste The person doing the interviewing and the physician directly supervising the patients have known the general nature of the medications for example that magnesium containing laxatives were being used and that one medication was a placebo but they have not known which medication was given to any particular patient at a given time The interviewer and supervising physician have also known when the medications were changed All medications were given out in coded boxes and the code was changed only once or twice during a study to prevent any fixed impressions of effectiveness from influencing the results

TABLE 2
PATIENT INTERVIEW FORM

Name________________ Number________________ Medication No.________________

Ward__________ Age__________ Sex__________

Activity	BED	WHEEL CHAIR	AMBULATORY

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
DAY																																
DATES																																
B M	0																															
	1																															
	2																															
	3																															
	3+																															
Consistency	Watery																															
	Soft																															
	Hard																															
Side effects	Gas																															
	Cramps																															
	Fullness																															
	Nausea																															
	Other																															
Well being	Good																															
	Fair																															
	Poor																															

Table 1
Treatment Schedule

No	Name	Rx	Date	Rx	Date	Rx	Date	Rx	Date	Rx	Date	Rx	Date
1		A		C		[illegible]		X		X		X	
2		B		F		C		X		X		X	
3		C		B		A		X		X		X	
4		D		E		F		X		X		X	
5		E		A		D		X		X		X	
6		F		D		B		X		X		X	
7		A		B		C		X		X		X	
8		C		F		B		X		X		X	
9		E		C		A		X		X		X	
10		B		D		F		X		X		X	
11		D		A		E		X		X		X	
12		F		E		D		X		X		X	
13		E		D		F		X		X		X	
14		B		C		D		X		X		X	
15		D		B		E		X		X		X	
16		A		F		C		X		X		X	
17		F		E		A		X		X		X	
18		C		A		B		X		X		X	

feces, (2) to ease defecation, and (3) to increase the number of movements. A determination of the number of bowel movements and the consistency of each movement should provide a means for measuring laxative action. A determination of weight, volume, water content, air content, or ease of defecation might also serve. The number and consistency were chosen because they could be easily determined by simply asking the patient each day. Consistency was determined by asking the patient whether each movement was hard, soft, or watery. To be sure, this involves a considerable source of variation, for what is soft to one patient may be hard to another and watery to a third. Moreover, the subjective report of consistency will be influenced by the ease of defecation and will not be a pure measure of consistency. We were not interested, however, in the absolute consistency but only in the change in consistency, and in this change only as a measure of a laxative effect. Hence the subjective inclusion of ease of defecation in consistency is an added step towards estimating laxative effect. Since each patient serves as his own control, variations in interpretation will even out and changes in consistency will provide a measure of laxative effect, albeit in one case it may be from hard to soft and in another, from soft to watery. The alternative of putting each stool in a vis-

TABLE 3
NUMBER OF BOWEL MOVEMENTS PER 6-DAY PERIOD

Patient	Lactose	Magnesium citrate	Milk of magnesia #1	Magnesium sulfate	Milk of magnesia #2	Patient totals
1	9	7	8	5	8	37
2	5	4	7	6	10	37
3	7	3	3	4	8	25
4	5	6	10	12	15	48
5	13	16	12	18	22	81
6	3	2	5	6	7	23
7	7	6	10	8	8	39
9	[illegible]	7	9	11	8	42
10	7	8	6	7	10	38
11	0	2	3	3	10	18
12	7	6	7	8	12	40
13	8	12	13	14	16	63
14	4	6	5	6	7	28
15	6	6	11	24	7	54
16	6	3	3	6	3	21
17	11	14	16	13	21	75
19	3	3	2	5	6	19
20	5	6	6	6	10	33
21	12	11	6	10	10	49
22	10	7	7	12	9	45
23	6	6	7	6	6	31
25	3	3	7	9	10	32
26	2	3	4	8	7	24
27	3	4	4	5	6	22
28	4	6	8	6	6	30
29	1	4	5	4	19	33
30	14	6	9	14	16	59
Totals	168	167	193	236	277	1041
Average number of movements per day	1.04	1.03	1.19	1.46	1.71	

lactose were about the same. The magnesium sulfate produced more movements than lactose, magnesium citrate, or the low dose of milk of magnesia and produced less movements than the high dose of milk of magnesia. These differences were statistically significant ($P < 0.05$). Accordingly, with the one reservation noted, both theories as to the mode of action of the magnesium-containing laxatives are wrong. All magnesium-containing laxatives given in equimolar doses are not equally effective, and magnesium sulfate is not twice as effective as milk *of magnesia*.

The analysis of the stool consistency data confirmed the foregoing conclusion but with a much higher degree of statistical significance. These data present a special problem in statistical analysis which will be reported elsewhere.

An interesting incidental observation concerned the time of day at which the movements occurred. TABLE 4 shows the percentage of movements which occurred during the night (from after supper, when the medication was given, until breakfast), during the morning (from after breakfast until lunch), and during the afternoon. Despite the fact that the high dose of milk of magnesia produced the most movements, these movements had no greater tendency to

cosimeter and quantitatively measuring its consistency in terms of centistokes in order to obtain an objective measure of laxative effect would be absurd for our purposes and to do this and neglect the basic principle of design would only serve to compound the absurdity

On the basis of the principles of design enumerated two laxative studies were made In the first one an answer was sought to the question "Is the laxative action of the magnesium containing cathartics solely attributable to their magnesium content? One of the well known textbooks of pharmacology[7] states that magnesium containing compounds are laxatives by virtue of the fact that the magnesium ion is not absorbed in the gastrointestinal tract hence it stays in the lumen in a soluble form retaining a certain amount of water in order to maintain isotonicity Inasmuch as magnesium ions in solution carry two positive charges there must also be present two negative charges on anions It makes no difference whether these anions can be absorbed or not They will be held in the gastrointestinal tract by virtue of the necessity for electrostatic equilibrium The increased water retained in the lumen of the gastrointestinal tract then acts as a mechanical stimulus to defecation Another textbook[8] states that magnesium sulfate is twice as effective as some other magnesium containing compounds such as magnesium citrate since it contains two ions which are unabsorbed instead of just one

To find out whether or not the magnesium ion alone determines laxative action five medications were used Three of the five medications served as a test of the first theory They were 5 1 gm of magnesium sulfate 4 82 gm of magnesium citrate and 1 2 gm of milk of magnesia all of which contain 0 5 gm of magnesium If the first theory is correct these should all give the same laxative effect Lactose and 2 4 gm of milk of magnesia completed the five medications They were included to test the second theory If the magnesium sulfate had twice the laxative action of milk of magnesia or magnesium citrate when given in equimolar quantities then its effect should equal that of twice the amount of milk of magnesia or magnesium citrate unless of course the laxative effects of the magnesium ion and sulfate ion were not independently additive This is a rather unlikely possibility but one which it would be easy to test in a separate experiment Since the bulk of the milk of magnesia dose was smaller than the magnesium citrate it was chosen as the one to be given in a double dose

The medications were put into eight green capsules all of which looked alike The patients took eight capsules every evening after supper At one week intervals the contents of the capsule were changed without the knowledge of the patient Patients were interviewed every morning by a nurse and the reports were recorded on the interview form illustrated in TABLE 2

TABLE 3 shows a tabulation of the number of bowel movements which occurred during the last six days of each medication The first day of medication was omitted since the mean for the first day was significantly different from that of the last six days by a Chi square test a carry over effect which may have been owing to residual medication in the gastrointestinal tract or to psychological factors

The mean number of bowel movements occurring on magnesium citrate and

Accordingly instead of the ideal study with nine medications it was felt that a practical answer could be achieved with six medications Three essentially equivalent designs are possible They are

(1) Lactose
  Bile Salts
  Bile Salts + Cascara Sagrada
  Bile Salts + Phenolphthalein
  Bile Salts + Cascara Sagrada + Phenolphthalein
  Caroid and Bile Salts with Phenolphthalein (total tablet formula)
(2) Lactose
  Cascara Sagrada
  Cascara Sagrada + Bile Salts
  Cascara Sagrada + Phenolphthalein
  Cascara Sagrada + Phenolphthalein + Bile Salts
  Caroid and Bile Salts with Phenolphthalein (total tablet formula)
(3) Lactose
  Phenolphthalein
  Phenolphthalein + Cascara Sagrada
  Phenolphthalein + Bile Salts
  Phenolphthalein + Bile Salts + Cascara Sagrada
  Caroid and Bile Salts with Phenolphthalein (total tablet formula)

TABLE 5
NUMBER OF BOWEL MOVEMENTS PER 6-DAY PERIOD

Patient	Lactose	Bile salts	Bile salts cascara	Bile salts phenolphthalein	Bile salts cascara phenolphthalein	Caroid & bile salts*	Patient total
1	6	6	9	9	6	2	38
2	10	15	11	9	14	14	73
4	11	12	12	9	12	12	68
5	0	2	3	1	2	8	16
6	6	4	7	7	16	7	47
7	5	6	9	11	11	10	5
8	5	5	8	4	9	8	39
11	1	0	0	1	2	3	7
12	6	5	8	9	7	10	45
13	11	1	20	17	18	20	98
14	6	5	10	14	11	1	47
15	4	5	4	3	4	3	23
16	5	6	5	8	10	8	42
17	14	9	14	17	16	15	85
18	4	5	2	6	7	5	29
19	6	5	6	6	8	6	37
20	6	6	9	6	6	6	39
21	[illegible]	6	8	10	12	9	52
22	6	6	6	8	7	7	40
23	4	1	5	9	12	8	39
24	6	5	8	12	14	16	61
25	6	[illegible]	7	8		5	40
26	9	4	7	4	11	[illegible]	44
27	1	3	2	5	6	4	21
29	1	1	4	4	6	5	21
30	14	17	14	14	14	17	90
Totals	160	158	198	211	243	218	1193
Average number of movements Per day	1.03	1.01	1.27	1.35	1.59	1.40	

* Total tablet formula.

TABLE 4

TIME OF DAY WHEN BOWEL MOVEMENTS OCCURRED

	Lactose	Magnesium citrate	Milk of magnesia #1	Magnesium sulfate	Milk of magnesia #2
Night	57.8%	56.0%	58.0%	67.4%	60.7%
Morning	39.2%	42.2%	39.4%	30.1%	35.6%
Afternoon	3.0%	1.8%	2.6%	2.5%	3.[illegible]%
Total Number of Movements	166	166	193	236	275

occur at night than did the movements on lactose. On the other hand, the number of movements occurring at night on magnesium sulfate was significantly different from that on the rest of medications, by a Chi square test. This would seem to imply that the conversion of insoluble milk of magnesia to a soluble magnesium ion capable of osmotically retaining water was a gradual process with the net result of a less strenuous but nevertheless efficient laxative effect.

In the second laxative study, an answer was sought to the question "Is the total laxative effect of Caroid and Bile Salts with Phenolphthalein Tablets owing to the additive effects of their content of dried bile, cascara sagrada, and phenolphthalein, or is there some modulation of the combined actions?"

Each "Caroid and Bile Salts with Phenolphthalein Tablet" contains the following:

Bile Salts Compound	1⅛ gr
Cascara Sagrada	¾ gr
Phenolphthalein	½ gr
Ext. Nux Vomica	1/16 gr
Capsicum	1/10 gr
Papain (Caroid)	1¼ gr

One might well expect that the first three ingredients would account for all the laxative effect.

A good way to test this expectation would be to use the following nine medications at dose levels, where possible, identical with that present in the complete product:

(1) Lactose
(2) Cascara Sagrada
(3) Bile Salts
(4) Phenolphthalein
(5) Bile Salts + Cascara Sagrada
(6) Bile Salts + Phenolphthalein
(7) Cascara Sagrada + Phenolphthalein
(8) Bile Salts + Phenolphthalein + Cascara Sagrada
(9) Caroid and Bile Salts with Phenolphthalein (total tablet formula)

If each patient, however, is to receive nine medications for one week, the study would run 2¼ months. During this period of time, one would expect, from experience in this type of work, that a significant proportion of the patients would drop out of the study for purely extraneous reasons. In the analysis of of variance, only those patients can be used who received every medication

Summary

(1) The value of the double blind and random sequence principles in the study of laxatives has been illustrated by two examples

(2) In one example it was shown that on an equimolar basis magnesium sulfate had a greater laxative effect than milk of magnesia or magnesium citrate but less of an effect than twice the dose of milk of magnesia On a weight basis milk of magnesia was more than twice as effective as magnesium sulfate

(3) In the second example it was shown that the total laxative effect of Caroid and Bile Salts with Phenolphthalein Tablets is not attributable to the simple additive action of cascara sagrada bile salts and phenolphthalein It would appear that the nonlaxative ingredients modify the effect of the laxative ingredients The exact nature of this modified action and the ingredients responsible for it must await further investigation

(4) The incidental observation was made that milk of magnesia in doses that produced more of a laxative effect appeared to have a slower onset of action than magnesium sulfate

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Discussion of the Paper

DOCTOR TRAVELL Would you mind saying at what hour the dosages were given?

DOCTOR SEED They were given half an hour to an hour after supper about

TABLE 6
ADDITIVE EFFECTS OF THREE LAXATIVES

	Movements per day	Increase in movement
$1\frac{1}{8}$ gr bile salts	1 01	0
$1\frac{1}{8}$ gr bile salts + $\frac{3}{4}$ gr cascara sagrada	1 27	0 26
$1\frac{1}{8}$ gr bile salts + $\frac{1}{2}$ gr phenolphthalein	1 35	0 34
		0 60
$1\frac{1}{8}$ gr bile salts + $\frac{3}{4}$ gr cascara sagrada + $\frac{1}{2}$ gr phenolphthalein		
Theoretical (assuming additive effects)	1 61	0 60
Actual	1 59	0 58

Any of these three designs would enable one to determine whether or not the result with the final formulation was the product of simple additive effects The first design was chosen since bile salts may take longer to produce an effect than the other laxatives in view of their property of recirculating through the intestine and liver It was felt that it might be desirable to maintain as nearly as possible a continuous background of bile medication In addition one would be able to determine whether there was any build up in the effect of the bile salts during the course of the study *i e*, the average laxative effect for all the medications including the bile salts might gradually climb during the study an effect which in actual practice did not occur

A tabulation of the number of bowel movements is shown in TABLE 5 The difference between bile salts + cascara sagrada + phenolphthalein (1 59) and ' Caroid and Bile Salts with Phenolphthalein (1 40) is not quite statistically significant at the 5 per cent level the actual probability of the same result on a random basis being 6 6 per cent However on analyzing the results from the more constipated patients (the best discriminators of laxative effects) the difference is significant One can thus say that in all probability the effects of the "Caroid and Bile Salts with Phenolphthalein Tablet are not attributable to simple additive actions of its ingredients but that the presence of papain nux vomica or capsicum in some way decreases the action of the rest of the combination

The bile salts + cascara sagrada + phenolphthalein produced the most movements which as can be seen from TABLE 6 is the result of the simple additive effect of the three ingredients The combination bile salts + cascara sagrada + phenolphthalein produced 1 59 movements per day and on the basis of additive effects one would have expected 1 61 The difference is not statistically significant or in terms of analysis of variance the interaction term is not significant

Accordingly the three principle laxative ingredients of Caroid and Bile Salts with Phenolphthalein have an independent additive effect but this is in important ways modified by the other nonlaxative ingredients There remains to be determined the therapeutic significance of this modulated diminished action

DOCTOR QUIGLEY As to the remarks made by Doctor Tainter I should like to say I feel quite certain that the action of milk of magnesia is by a somewhat different mechanism than that involved in the action of magnesium sulfate as indicated by the fact that the response to the administration of magnesium sulfate may occur within 15 minutes or half an hour while a number of hours eight hours and such time may be required for the action of milk of magnesia I think if you want to compare the action of magnesium ion you might get better results by using magnesium chloride which is formed when the acid of the stomach acts on magnesium oxide I think we need the magnesium ion present in the same concentration in the upper intestinal tract in a certain time and a mass of magnesium ions present in the same concentration in the upper intestinal tract to obtain comparable effects It is an indication that magnesium sulfate present in the upper intestinal tract in concentrated form may initiate reflexes which may start locally and bring about more distal reflexes which are emphasized by some of the effects that may occur almost simultaneously in the upper intestine and colon Certainly you would lose that if the magnesium ion were given in the form of the oxide which changes into chloride and is changed into it very gradually This is an aspect of the study that needs further consideration

QUESTION I am confused by your conclusions about the 1 49 and 1.52 I thought as you presented that table that it looked as if everything was adding up very nicely and you had accounted for the action of the Caroid and Bile Salts and Phenolphthalein mixture on the basis of the individual ingredients To the casual eye it would look as if 1 61 and 1 59 were not significant and I thought you said they were significant and then turned around and concluded there was importance in the other ingredients or in the mixture of the substances

DR SEED I am sorry if I confused the matter Cascara sagrada plus phenolphthalein plus bile salts produces an effect which can be explained by the additive action of all three When you add to that however caroid plus nux vomica plus capsicum to get the Caroid and Bile Salts with Phenolphthalein formulation you then get a decreased number of movements You get the 1 40 instead of 1 59 So there is something either in the caroid nux vomica or the capsicum which in some important way is modifying the action of cascara bile salts and phenolphthalein

five or six o'clock For this group, breakfast occurred about eight o'clock in the morning, the observation 8.30 to 9.00

CHAIRMAN CATTELL Your results showed more frequent evacuation with the magnesium hydroxide?

DOCTOR SEED Magnesium sulfate gave the highest and most rapid action on a molar basis, magnesium on a weight basis

DOCTOR INGELFINGER What sort of patients did you use, and how many bowel movements a day according to your figures did they have when you gave them nothing?

DOCTOR SEED We did not measure the movements they had when we gave them nothing Our lactose was 1 03 movements per day, which is not the same thing but is our closest estimate The patients consisted of men from an old folks home in the Albany area The average age of the group was 69 to 72 one study 69, and the other 72 By and large, most of the patients had complaints of one sort or another related in their minds to constipation That is why they were willing to participate in the study They felt unhappy about their bowel status and about the number of movements, even though they may have been having one movement a day

CHAIRMAN CATTELL Actually they were not necessarily particularly constipated if they had one movement a day

DOCTOR SEED That is true and one movement a day is an average for the group Some patients however, had only one movement a week and hence *were truly constipated by the usual definition*

DOCTOR TAINTER As a pharmacologist teaching groups of medical students over many years I sneered and arched my eyebrows about the old fashioned compound laxatives Later I found to my amazement that these old fashioned preparations as a matter of fact were very popular and very widely used and not decreasing in use as might be inferred by some of the discussions For example, Caroid and Bile Salts preparation was mentioned If my information is correct it is steadily increasing in general use and not in response to special new promotional activities but rather it is finding some kind of improved or increased acceptance by the public That poses a problem to the pharmacologist to know why this is so because according to the old concepts the formulation might be considered irrational since it has ingredients whose actions are not understood or how they contribute to the total effect Fortunately by these new powerful statistical tools we are now able to separate the actions and find out whether these ingredients do contribute to the action Doctor Seed has made the first systematic attempt to do this and we find in fact there are results that you cannot predict from the known laxative ingredients We have therefore to study these compound preparations much more carefully than we have ever done before I think that Doctor Seed by pointing out to us that these techniques are applicable and that you can get reliable differences in results has given us the stimulation to go ahead and study such therapy in even greater detail until finally we shall find out why the actions of mixtures of these materials are so different from what we would predict from the individual ingredients

TABLE I

TYPES OF COLLOIDAL LAXATIVES

(1) Bentonite clays
(2) Dried fruits and vegetables
(3) Marine algae
  (a) Agar agar
  (b) Sodium alginate
(4) Gum acacia
(5) Locu t bean gum
(6) Tragacanth gums
  (a) Cassorin
  (b) Bassora gum
  (c) Karaya gum
(7) Psyllium
  (a) *Plantago psyllium* (black psyllium seeds)
  (b) *Plantago arenaria* (Spanish or French psyllium seeds)
  (c) *Plantago ovata* (blond or Indian psyllium seeds)
(8) Synthetic derivatives of cellulose
  (a) Methylcellulose
  (b) Sodium carboxymethylcellulose

from the mall intestine of the cat A lack of irritation in isolated loops of the intestine *in situ* was demonstrated when bassorin was introduced under anesthesia Patients taking bassorin for the relief of constipation passed soft haped stools The increased water content rendered the feces softer and therefore lessened the resistance offered to the intestinal mucosa It is also responsible for the increase in intestinal volume which stimulates the peristaltic tension reflex clinical observations leave no doubt that bassorin will relieve constipation and that it will do so without causing digestive disturb ances the distinction between bassorin and agar is very marked Bassorin is considerably more effective than agar

In 1938 Ivy and Isaacs[8] reported that karaya gum not only takes up more water than agar but that it also holds more firmly Feeding studies were carried out in dogs which showed that approximately 95 per cent of the ingested gum was excreted in the feces They also studied the effect of karaya upon nitrogen utilization in dogs They conclude it is our belief that bulk provided by Karaya may under some conditions influence food nitrogen assimila tion but that the amount which would be used for therapeutic purposes probably would not provide bulk of sufficient magnitude to interfere significantly with this important metabolic activity It was found that karaya did not apparently affect starch digestion in dogs receiving an essentially high starch diet and did not inhibit the utilization of vitamin A in rats Karaya in its unprocessed and processed forms produced an increased number of defecations increased bulk and moisture but did not cause detectable irritation It was administered in the form of granules sold as Mucara to 89 subjects This increased the bulk of the stools in 80 8 per cent of the human subjects studied increased the moisture content in 75 2 per cent increased the number of defecations in 53 9 per cent and increased the urge to defecate in 42 7 per cent It relieved constipation in 19 of 23 persons studied Ivy and Isaacs conclude Mucara produces no harmful effects nor is it habit forming if taken over long periods of time The evidence suggests its value as a regulator of bowel habit

QUANTITATIVE COMPARISONS OF COLLOIDAL LAXATIVES

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The colloid laxatives may be classified into eight general groups as shown in TABLE 1

The more important of these colloid laxatives are discussed below followed by a review of quantitative *in vitro* and *in vivo* studies comparing the various materials

Tragacanth

Tragacanth is one of the oldest reported drugs It was described by Theophrastus, who lived in the third century B C by Dioscorides and by many Arabian medical writers It was imported into Europe through Italian trading cities in the middle ages It has been official in each edition of the U S P since 1820

Tragacanth appears to be composed of two different components the one resembling gum arabic and dissolving in water the other swelling in water but without dissolving The soluble part (the greater portion) is composed chiefly of polyarabinan trigalactan geddic acid which yields on hydrolysis arabinose galactose and geddic acid The insoluble substance is mostly bassorin which swells in water to a large bulk Closely related to tragacanth are the bassora and karaya gums which come from the bark of trees of the genus *Astragalus* (Family Sterculiaceae)

In 1924 Schindler[1] reported the successful treatment of constipation with a commercial bassorin product Normacol The wet weight of the stools increased about 2½ times when 10 gm of the laxative were given twice daily Schindler demonstrated with X rays that bassorin accelerates the passage of the intestinal contents Tost in 1925 reviewed the properties of this product and showed that it does not influence peptic and pancreatic digestion He treated two patients suffering from constipation with it and both were relieved and passed soft formed stools within a short time

Porges[3] reported in 1928 that he had used the preparation of bassorin mucilage extensively in cases of simple chronic constipation as well as in psychogenic and habitual types of constipation In my opinion the treatment of chronic constipation by this means should form a particularly valuable addition to the physician s armamentarium Berg reported studies in dogs and humans with the bassorin containing Normacol in 1930[4] The administration of 25 gm to a dog caused an 11 per cent increase in the water content of the stools The administration of two teaspoonfuls in self experiments produced an 11 per cent increase in the wet weight of the stools Berg also showed that bassorin will overcome the constipation produced by tincture of opium

Parson in 1932[5] reported that bassorin had no adverse effects upon either peptic or tryptic digestion and that it did not delay the absorption of glucose

stipation both of the atonic and spastic forms Tonicity and peristaltic action of the colon were increased and the haustral markings neared the normal Defecation and the feeling of urgency increased The general sense of well being of the patients was improved Stein and Gelehrter concluded that when natural methods for the correction of constipation, such as exercise regularity of defecation times and proper diet do not adequately alleviate functional constipation the use of hydrogels is the most efficacious treatment because of their power to increase the bulk of the intestinal contents

Ivy and Isaacs[8] in 1938 reported studies in dogs with a Psyllium loeflingii ' Mucilose Five grams of Mucilose per day softened the stools and increased their number per day The total bulk of the stools was increased by 49 per cent and the moisture content was increased by 54 per cent

Quantitative studies in human subjects by Gray and Tainter[8] in 1941 showed that the psyllium preparations studied definitely increased the daily average fresh weight of the stools Whole psyllium seeds decreased the water content of the stools but the ground derivatives of psyllium increased the water content by an average of 3 7 per cent as compared to a value of 2 1 per cent for various tragacanth gums Whole psyllium seed increased the dry weight by an amount almost equal to that predicted on the basis of no intestinal breakdown In contrast the psyllium products in which the seeds had been ground up and the hemicellulose used in a partially purified form did not increase the dry weight in proportion to the amount administered The authors therefore believe that the processed psyllium products may be partially broken down in the digestive tract to stimulating end products which contribute to the laxative properties of the preparation

Block[25] in 1947 reported a study of the clinical effectiveness of a commercial preparation (Metamucil) composed of 50 per cent refined mucilloid of the psyllium seed (*Plantago ovata* Forsk) and 50 per cent powdered anhydrous dextrose In a series of 40 subjects this laxative was found to be effective in both the atonic and spastic types of constipation especially in the latter form Roentgenologic study disclosed that the gastrointestinal tract emptied more rapidly following the ingestion of the laxative Patients reported relief of bowel and anal spasm pain and tenesmus during the test period

Cass and Wolf[26] in 1952 carried out a comparative study of the laxative properties of psyllium and methylcellulose in 101 patients from a notoriously refractive group of hospitalized elderly males and females having chronic diseases psyllium seed preparations proved considerably more effective than methylcellulose as a bulk laxative and were also superior to previous laxatives such as milk of magnesia mineral oil cascara or a phenolphthalein ipecac preparation In the severe types of constipation from 73 to 82 per cent of patients were improved on psyllium therapy

Methylcellulose and Sodium Carboxymethylcellulose

The use of synthetic colloidal materials derived from cellulose as bulk producing laxative agents was suggested by Tainter[27] who reported the first clinical use of methylcellulose in 1943 Sodium carboxymethylcellulose was first used clinically as a bulk laxative in 1948 by Fittipoldi and Davis[28]

Methylcellulose is a white light fluffy material which is sold in different

Bargen[7] stated in 1939 'Clinical experience suggests that karaya gum is the best mechanical aid to intestinal evacuation on the market today and that it *has value in some forms of diarrhea as well* "

Gray and Tainter,[8] in 1941, studied the laxative effects of tragacanth and karaya in human subjects A definite increase in total daily fresh and dry weight and the percentage of water in the feces was observed The tragacanth derivatives appeared to pass through the gut without being broken down and thus exerted their laxative actions primarily through colloidal swelling

A number of adverse side effects from the use of these preparations have been reported Goldman[9] reported esophageal obstruction in a patient who had ingested a large quantity of a bassorin product and Waud[10] reported a fecal impaction It has been found that karaya may lead to hypersensitivity causing perennial hay fever,[11] asthma [12, 13] atopic dermatitis,[14, 15] urticaria [16] and migraine [13] Figley[14] alone observed sixteen cases of hypersensitivity to karaya gum Gelfand[18, 19] has reviewed the etiology of allergic disorders with reference to vegetable gums especially tragacanth and karaya

Psyllium

Fluckiger and Hanbury [0] describe the use of psyllium or fleawort as early as the tenth century in the Orient It was known to Europeans toward the close of the 18th century Fleming listed it in his 'Catalog of Indian Medical Plants and Drugs in 1810 under the name, Ispaghul Psyllium was admitted to the pharmacopeia of India in 1868 Although plantain seeds have been used medicinally in Europe and Asia for several centures they did not come into common use in the United States until the second decade of the present century

Psyllium derivatives yield a copious amount of natural mucilage and swell in the bowel forming an emollient indigestible mass Schindler in 1924 [1] and Klecker, in 1931 [1] found that psyllium is less hydrophilic than agar and bassorin Bastedo[2] reported that whole psyllium seed swells about 10 times and hulled psyllium 14 times more in water than flaked agar whereas bassorin swells to 29 times as much as agar The psyllium derivatives were found to be one half as hydrophilic as the tragacanth gums by Gray and Tainter [8] Blythe Gulesich and Tuthill [3] reported that the relative efficacy of the psyllium preparations varied widely with the source and brand of product In general the psyllium perparations appeared to be slightly less or equal to the tragacanth gums in hydrophilic and 'water holding capacity but less than the synthetic cellulose derivatives

Stein and Gelehrter [4] in 1940 reported a study of the epidermal tissue of *Plantago ovata* (in the form of Serutan) in the treatment of functional constipation in 22 patients This laxative was reported to absorb about 20 times its weight or 16 times its volume of water The authors selected patients with functional constipation using as controls one normal patient and two having cases of colonic malignancy At the beginning and end of the investigation X ray studies following barium enemas were made in all cases The dose administered to each patient was 1½ teaspoonfuls twice daily in water followed by another glass of water over a period of 14 to 130 days The investigators adjudged the product to be of real value in the treatment of functional con

soft bulky stools without griping cramping or tenesmus in most cases Its prolonged use up to eight months produced no evidence of systemic changes or toxicity Bargen[47] reported the treatment of 36 patients with methylcellulose and stated Function of the bowel can be greatly improved by the addition of methylcellulose appropriately prepared in such conditions as the syndrome of irritable bowel associated with either constipation or diarrhea intestinal stomas and the milder forms of intestinal infections associated with diarrhea The use of methylcellulose does not constitute a so called cure for the several intestinal dysfunctions discussed It represents a valuable addition to a well ordered program of medical care for the conditions mentioned which often constitutes the difference between happiness and unhappiness of the individual afflicted with that symptom

Marks[48] studied the laxative effects of both methylcellulose and sodium carboxymethylcellulose in 2/0 patients Methocel proved to be a far more satisfactory colloidal laxative than any bulk material previously used for correction in constipation The physiological action of this material produced well formed stools of unusually soft consistency as a result of the superior water retaining properties of this synthetic colloid Functional constipation was successfully treated with methocel and psychotherapy It was found possible to wean patients away from their use of harsh cathartics and displace them with the colloid laxative Patients who have been taking the synthetic colloids for as long as 18 months have not experienced any undesirable side effects such as bowel irritation or allergic reactions Tablets and granules made up of the lower viscosity forms of methylcellulose and carboxymethylcellulose were found to be equally effective in producing normal soft stools

Seventy patients with chronic constipation were treated with methylcellulose by Newey and Goetzl[49] The material used was of beneficial effect in most patients suffering from rectal constipation and in a large number of patients suffering from constipation due to spasticity of the colon Atony of the bowel *apparently required more stimulation than was provided for by the* methylcellulose in the amounts used In addition it was noted that methyl cellulose may be of value in re establishing normal stool habits Musick[50] found methylcellulose to be a useful adjunct in the control of constipation in 80 per cent of 102 cases

The comparative effectiveness of methylcellulose and psyllium seed was studied in hospitalized elderly patients having chronic disease by Cass and Wolf[26] As mentioned above these workers reported that psyllium seed preparations proved considerably more effective than methylcellulose as a bulk laxative Tudbury[51] reported good and excellent results in 18 of 24 patients With atonic constipation only two of nine patients showed improvement Tudbury states that the atonic bowel appears to need a chemical as well as a mechanical stimulus to correct its failure to function

Fittipoldi and Davis[3] studied the clinical effectiveness of sodium carboxy methylcellulose in 128 patients and reported good laxation with no side reactions in 109 of their cases They concluded that this synthetic colloid appears to be an effective and safe bulk laxative for clinical use Blake[45] studied sodium carboxymethylcellulose in 35 subjects with good results in the 25 pa

grades of viscosity and is being used in large quantities in the food industry and in the manufacture of pharmaceuticals as a thickening and emulsifying agent It is a partially depolymerized cellulose in which an average of two methyl radicals are held in ether linkage on each glucose unit [29] Sodium carboxymethylcellulose occurs as a white powder or granules which first became commercially available in this country as a pharmaceutical in 1947 [30]

These two synthetic materials have been claimed to be superior to the natural gums in several respects They are nontoxic when given orally, are not absorbed by the intestinal mucosa are not degraded by intestinal enzymes and are nonantigenic [31] They do not interfere with the intestinal absorption of fat soluble vitamins and are unlikely to produce an impaction They have a high degree of chemical uniformity and can be readily compressed into tablets a form of administration which many prefer to powders or granules [3] Schultz[33] emphasizes that these synthetic colloids are tasteless and odorless, that they contain no roughage to irritate delicate mucous membranes that they have marked lubricating properties and in cases of diarrhea they have an apparent ability to absorb irritating toxins from the intestinal tract

In vitro studies on the hydrophilic and water retaining properties of methyl cellulose and sodium carboxymethylcellulose have been reported by Tainter,[27] Blythe Gulesich and Tuthill[28] and Berger Ludwig and Wielich [34] The results of these studies are discussed in detail below

(1) *Toxicity studies* Chronic toxicity studies in rats by Tainter [27] Deichmann and Witherup [35] and Bauer Lehman and Yonkman[36 37 33] have shown that methylcellulose is nontoxic when fed to animals over prolonged periods of time Machle Heyroth and Witherup[39] have observed that methylcellulose passes through the human digestive tract virtually unchanged since it is recovered almost quantitatively from the feces Schweig[40] found that the prolonged administration of methylcellulose to human subjects for eight months produced no evidences of systemic toxicity Laboratory data on acute chronic and life time feeding studies in rats guinea pigs rabbits and dogs by Werle [41] Brown and Houghton [4] Rowe Spencer Adams and Irish[43] and Shelanski and Clark[44] show that sodium carboxymethylcellulose is nontoxic and produces no gross or microscopic pathology when fed over prolonged periods of time Studies by Blake[45] have shown that the oral administration of sodium carboxymethylcellulose for several months produced no deleterious effects on important body functions such as blood formation liver and kidney functions *etc*

(2) *Clinical studies* Methylcellulose alone and in combinations with magnesium oxide powder or finely milled bran was studied in human subjects by Tainter [3] He found that 10 gm per day of methylcellulose approximately doubled the volume of the stools and increased their frequency in normal human subjects Each gram of ingested methylcellulose increased the stools approximately 10 gm Lehman [46] in 1945 reviewed the literature on bulk laxatives and concluded that there were no clear cut correlations between the hydrophilic properties of the gums and their laxative action

The treatment with methylcellulose of 37 patients suffering from acute and/or chronic constipation has been reported by Schweig [40] Doses of 1 to 6 gm daily proved effective for relief in 92 per cent of the cases giving normal

TABLE 3

VOLUME OF GEL FORMED BY 5 GRAMS OF THE COLLOIDS IN VARIOUS SOLVENTS

Group	Average swelling of gels (after 24 hours)			
	NaCl 2%	Distilled H_2O	HCl 0.5%	$NaHCO_3$ 1% cc
Agar pd	65	85	60	65
Acacia pd	20	15	15	25
Tragacanth (processed)	130	291	115	161
Psyllium (processed)	98	105	89	105
Methylcellulose[27]	—	200	—	—

proached *in vivo* conditions These data showed that powdered acacia swelled relatively little whereas agar swelled to about six times its original valume The members of the tragacanth family swelled very markedly but the psyllium derivatives swelled only about one half as much as the tragacanth From these results and other *in vitro* swelling properties it may be anticipated that the processed members of the tragacanth family may increase the bulk about 20 times and the psyllium derivatives about 10 times in the intestine

Tainter[27] reported the first quantitative data on the *in vitro* swelling properties of methylcellulose Five gm of methylcellulose swell in a 500 cc graduate of distilled water to about 200 cc the final volume depending on the fineness of the powder thoroughness of wetting *etc* If complete wetting occurs the compound disperses completely giving a thick solution of gel Swelling is not materially modified by concentrations of hydrochloric acid sodium bicarbonate or sodium chloride such as it might come in contact with in the body

Quantitative *in vitro* studies on the hydrophilic properties of various bulk laxatives including methylcellulose and sodium carboxymethylcellulose have been reported by Blythe Gulesich and Tuthill[28] These workers emphasized that Three properties are significant in the *in vitro* evaluation of bulk laxatives (a) the volume of water absorbed in various media (water and artificial gastric juices) (b) the viscosity and texture of the gel formed and (c) the ability of the gel to retain water They reported that the karaya and psyllium type substances swell much better in water than in artificial physiological fluids In the simulated gastric juice they attain roughly half the volume obtained in water and in artificial intestinal juice they swell more than in the acidic medium but less than in water The cellulose derivatives on the other hand dissolve equally well in water or in artificial intestinal fluid In the artificial gastric juice however the sodium carboxymethylcellulose is converted to the free acid which is insoluble Methylcellulose on the other hand becomes partly swollen and floats on the surface of the media

Blythe *et al* discussed the viscosity and texture of the gels formed by various materials The cellulose derivatives form a clear viscous solution Karaya products swell in the various liquids to form gels which retain their granular texture Psyllium products may be classed between these two extremes Whole psyllium seed forms gelatinous masses with the inner part of the seed

tients reporting. There were no subjective side reactions and no evidence of impaction was observed. Schultz[33] studied sodium carboxymethylcellulose in over 250 patients having various degrees of constipation. All were markedly benefited by the use of small amounts of sodium carboxymethylcellulose. "We found this synthetic gum to possess most of the advantages and none of the disadvantages of the other cathartics heretofore available to us."

Quantitative Comparison of Colloid Laxatives

(1) *Quantitative in vitro studies.* In 1924, Schindler[1] reported that, *in vitro* the swelling properties of bassorin gum exceeded those of psyllium and flax seeds. Klecker[21] in 1931 measured the swelling capacity of several fruits and gums. Tamarind pulp, dried prunes, dried apples and wheat bran swelled very little. Psyllium seed and flaxseed swelled to three times and agar increased to six times the initial volume. The greatest swelling was obtained with bassorin gum, *i.e.*, in water to the tremendous bulk of 44 times the initial volume, in dilute alkali, 38 times, and in dilute acid, 10 times. Parson[5] reported, in 1932, that chopped agar expanded to about 2½ times its volume in distilled water, and that one gram of bassorin absorbed 28 cc. of distilled water. He concluded that bassorin has about twice the hygroscopic properties of agar.

Bastedo[22] in 1935 reported studies on the comparative swelling properties of various natural gums in water which are summarized in TABLE 2.

The abilities of karaya and agar to absorb water were compared in 1938, by Ivy and Isaacs.[6] These workers found that when 1 gm. of karaya was added to 100 cc. of distilled water at 20° C., it started to swell at once and within 20 to 30 minutes the beaker containing it could be inverted without spillage of the contents. Measurements showed that the karaya gum will imbibe 90 per cent of the water and that an equal weight (1 gm.) of ground agar will imbibe 71 per cent of the water.

In 1941 Gray and Tainter[8] carried out comparative quantitative *in vitro* studies on the hydrophilic swelling of various materials under conditions similar to those in the gastrointestinal tract. The volumes reached at the end of 24 hours are summarized in TABLE 3, thus permitting a comparison of their swelling capacity.

Inasmuch as the lower intestine, where the greater part of the swelling presumably occurs, is more nearly neutral than either highly acid or alkaline, it was felt that the results with the 2 per cent sodium chloride more closely ap

TABLE 2
RELATIVE SWELLING PROPERTIES OF VARIOUS GUM LAXATIVES

Material	Relative swelling properties
Dried flaked agar	1
Granular agar	3
Powdered agar	5.5
Whole psyllium seed	10
Hulled psyllium	14
Bassorin	29

In 1924, Schindler[1] reported studies in patients with a bassorin preparation Ten grams twice daily increased the wet weight of the fresh stools from 80–95 gm. to 155–190 gm A return to the control diet reduced the stool weight to 95 gm Experiments on the laxative properties of various foodstuffs and agar were carried out in medical students by Williams and Olmsted in 1936 [54, 55] Ten gm of agar per day caused a marked increase in basal stool weights A total of 80 2 gm of agar fed to each of three students gave a seven day average increment in stool weight of 666 gm or an increment to residue fed ratio of 8 30 Studies in 89 human subjects by Ivy and Isaacs[8] showed that the daily administration of one heaping teaspoonful of Mucara (approximately 7 gm. of karaya) per day resulted in an increased weight of the stools during the first five days medication of between 15 gm (2 4 per cent) and 922 gm (293 6 per cent)

Gray and Tainter[8] in 1941 attempted to assess the clinical value of various colloidal laxatives according to the following criteria frequency of defecation size of the individual stools total daily bulk of fecal material and fluidity or physical state of the mass These phenomena were observed in five volunteer human subjects who remained on a normal diet and at their usual activities Their fluid intake was held as nearly normal as possible without imposing quantitative control The stools were collected quantitatively during the last three days of each week After the first week with its control collections there followed a week during which each subject took 5 gm of the laxative each morning washed down with one glass of water The stools were collected during the last three days of this week as in the first week During the third week, no laxative was taken but a second collection of control stools was obtained the last three days In this way control periods without medication were alternated with periods when laxatives were taken until each of a selected group of the colloids had been taken by each subject The stool specimens were collected only during the last three days out of each seven in order to allow time for establishing an equilibrium under the conditions of the tests The wet weights of the stools were recorded and the stools were dried at 110 C From the dry weights the water content in grams and percentage were determined by difference

The average daily weight of stools was 91 gm during the control periods During the administration of the laxatives this weight was 113 gm i e a significant increase of 22 gm daily Inasmuch as only 5 gm of the laxative was administered daily there was a net increase in the stools about four times greater than that of the dry weight of the administered laxative Therefore all of these agents increased the daily bulk of the stools by an amount considerably in excess of their dry bulk However the actual changes in total weights of the stools were considerably less than would be predicted from results *in vitro* These colloidal laxatives therefore did not swell to their full theoretical extent under practical conditions

The percentage of water contained by normal stools may vary considerably from individual to individual Because of this wide individual variation the standard errors were also abnormally large In order to obtain significant results it appeared best if the comparisons of the water content were made from

retaining much of its form The hemicellulose materials derived from psyllium give viscous, pourable, opaque gels with widely varying amounts of insoluble seed material remaining depending on the brand of product' Blythe *et al* also studied the retention of water in a specifically designed osmometer which measured the ability of a sol or gel to hold water against the osmotic pull of a hypertonic solution of 30 per cent Carbowax 4000W when the two media were separated by a semipermeable cellophane membrane The cellulose derivatives were clearly superior in osmotic pull The efficacy of the various karaya and psyllium preparations differed widely with the source and brand of the product tested

Berger, Ludwig and Wielich[5] [34] have recently published studies on the hydrophilic and acid binding properties of sodium alginate in comparison with other bulk laxatives They state 'After examining a number of compositions made by dispersing these materials in water in various proportions it did not appear feasible to use their bulking capacity as a valid means for evaluating the water retaining ability This is primarily because of the different behavior exhibited by the various materials when dispersed in water The seaweed colloids and the modified cellulose products produce a viscous continuous type of mucilage in contrast to the discontinuous gel formed by the plant seeds and gum exudate products It was found however that the method of Blythe *et al* [23] which measures the water retaining capacity against a standard osmotic pull is more suitable for the evaluation of the relative water retaining capacity of bulk laxatives Sodium alginate was found to possess greater water holding capacity than any of the other materials tested Carboxymethylcellulose and methylcellulose although not as effective as sodium alginate possessed considerably greater water holding action than products from psyllium and gum karaya Berger Ludwig and Wielich pointed out that the experimental procedure devised by Blythe was subject to an inherent limitation so that a method that simulated more closely the conditions prevailing in the digestive tract was evolved By this test sodium alginate was observed to be superior to other bulking substances in its water absorbing potency The products derived from psyllium seed and karaya were again poorest in this respect while methylcellulose and carboxymethylcellulose occupied an intermediate position A 3 per cent solution of sodium alginate had a water absorbing capacity equivalent to an 8 per cent solution of carboxymethylcellulose and to a 10 per cent solution of methylcellulose Psyllium seed and karaya even when present in concentrations greater than 10 per cent were inferior to 2 per cent solutions of sodium alginate and the cellulose products However it should be pointed out that the apparent *in vitro* superiority of the alginate might not carry over to *in vivo* conditions unless it could be shown that the alginate resists digestion and absorption as completely as do the cellulose derivatives and the two plant gums

(2) *Quantitative in vivo studies* Schmidt [63] in 1905 reported what appear to be the first human quantitative studies on the use of agar as a laxative He observed a more than two fold increase in wet weight and an increase in dry weight and cellulose that was practically equivalent to the weight and cellulose content of the agar fed

TABLE 4
CLINICAL STUDIES ON EIGHT SUBJECTS COMPARING METHYLCELLULOSE PSYLLIUM COMBINATION TABLETS WITH PLAIN METHYLCELLULOSE TABLETS[11]

	Over-all controls averaged	Methylcellulose		Compound tablets			
		9 tablets per day (4.5 gm)		6 tablets per day (3.0 gm)		9 tablets per day (4.5 gms)	
		N	Increase	N	Increase	N	Increase
No stools per day	1 30	1 51	0 21	1 57	0 27	1 48	0 8
Avg wet wt. per day (Gm)	162 9	189 7	26 8	183 7	20 8	213 1	50 2
Avg dry wt. per day (Gm.)	32 0	37 8	5 8	34 9	2 9	37 8	5 8
Avg water content (%)	80 42	80 07	−0 35	81 0	0 58	82 26	1 84
Avg wet wt. per tab (Gm)			2 98		3 47		5 58

reported[9] with gum karaya and psyllium showed that gram for gram methyl cellulose had greater effect than these other laxatives

Methylcellulose Psyllium Combinations

A combination of psyllium and methylcellulose should theoretically add the advantages of the sponge like absorption and retention of water by the psyllium gum to the bulk laxative effects of the viscous demulcent liquid formed by dispersion of methylcellulose in the liquid contents of the intestines Such combinations have been studied recently and three methylcellulose-psyllium formulations are now available commercially which contain 0 4 gm of methylcellulose and 0 1 gm of purified psyllium hemicellulose *

Berberian Pauly and Tainter[11] have published the results of clinical studies in human volunteers comparing these methylcellulose psyllium combination tablets with plain 0 5 gm methylcellulose tablets The principles of the stool weight method of evaluation of Gray and Tainter[9] was used with eight volunteers on regular diet serving as subject Stools were collected each day for one week as a control period which was followed by one week of medication with nine tablets of methylcellulose per day in divided doses Another week of control stools was collected succeeded by a week of medication with six of the compound psyllium methylcellulose tablets per day in divided doses After another intervening control week medication with nine of the compound tablets per day was carried out for a week followed by a final week of control The results of these studies are summarized in TABLE 4 Inspection of TABLE 4 shows that the subjects excreted an average of 162 9 gm of stools per day when not receiving medication Nine tablets of methylcellulose increased the bulk of the stools by 26 8 gm per day which was an average of 1 98 gm per tablet administered The compound tablet of the same weight but containing

*Mucilose Compound Tablets Winthrop-Stearns Inc Pla ll American Ferment Company and Pla lo Winthrop Products Inc

the changes in each individual subject between his control and experimental periods Therefore the average water content of the stools of each individual during his control periods was compared with the water content when the drug was taken

The processed derivatives of psyllium increased the water content by an average of 3 7 per cent The tragacanth group of products caused an average increase in water content of 2 1 per cent These changes in water content may seem rather small in terms of absolute magnitude but they are not small in actuality since the water content of unformed fluid stools was only about 10 per cent greater than that of the hardest formed scybala An increase of 2 to 3 per cent in the water content therefore represents a considerable softening and increase in the fluidity of the feces

Gray and Tainter concluded their report by pointing out that black unground psyllium seed produced a constipative effect as shown by less frequent defecation and firmer bulkier stools of diminished water content The other preparations did not alter appreciably the frequency of passages The tragacanth products did not appreciably alter the size of the individual stools but increased the total daily wet and dry weights and the percentage of water in the feces The gain in the daily dry weight was almost exactly that of the dry gum administered, indicating that the tragacanth passed through the gut without being broken down

The processed psyllium products also do not appreciably alter the weight of the individual stools All three products however, increased the total daily bulk of the stools to a moderate degree, and the water content by an average of 3 73 per cent This increase in fluidity was nearly double that produced by the tragacanth products The dry weights of the stools were not much increased by the psyllium products indicating that their hemicelluloses were at least partially broken down in the intestine to irritant but semiabsorbable materials, as has been suggested previously

Tainter[27] in 1943 reported the first studies on the laxative effects of methyl cellulose in man Methylcellulose, alone and in various combinations with magnesium oxide powder and finely milled bran was taken in the form of fine flakes by three subjects All subjects maintained a constant diet and collected their stools quantitatively The average wet weight of stools on the control days was 127 4 gm with approximately one evacuation a day When methyl cellulose was mixed with various proportions of bran or with 3 5 or 10 per cent magnesium oxide the number and volume of the stools were moderately increased Methylcellulose alone in a dose of 5 gm twice daily increased the number of stools to 1 6 per day and the wet weight to an average of 232 1 gm a day This represented a stool volume almost twice the control The methyl cellulose stools had a slightly higher water content than the controls and were semisoft and easy of passage The averages indicated that each gram of methylcellulose increased the bulk of the stools about 10 gm The greater part of this increase was water held by the colloid although the dry weight increased somewhat more than could be accounted for by the dry weight of the methyl cellulose administered Comparison of these results with those previously

Summary

The studies reviewed in this discussion make it clear that important increases in colonic activity can be induced by giving colloidal gums of several types The relative activity of individual products can be approximately predicted from their colloidal properties as revealed *in vitro* These materials do not interfere with digestion or assimilation

New interest was aroused in this group of compounds by the introduction of the cellulose derivatives which could be compressed into tablets With the observation that useful amounts of psyllium can be incorporated with methyl cellulose a substantial increase in potency has been achieved It seems likely that this type of combined medication will gain in use as knowledge of its added therapeutic value becomes more widespread

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the balanced combination of bulk laxative ingredients, increased the bulk of the stools by 20 8 gm on a dose of six per day and 50 2 gm on a nine tablet dose The overall average increase from the compound tablet was 4 73 gm per tablet administered In the nine tablet a day dosage range, however, each tablet of the compound formula produced an increase in bulk of 5 58 gm or 87 per cent more than the straight methylcellulose tablets The exact values of these ratios of activity should not be overemphasized because of the inherent variability of the experimental set up, but their order of magnitude is quite reliable inasmuch as observations covering 366 patient days make up these averages

These figures clearly establish that the compound formula has an enhanced laxative power since it produces an increase in stool weight of 4 73 gm per tablet, as compared to only 2 98 gm for the plain methylcellulose tablet This increased effectiveness permits either greater action from the full nine compound tablet dosage regime, or practically the same degree of effect from only six tablets per day as is observed with nine of the plain methylcellulose tablets

A distinct lag in the onset of action of the simple tablet, as compared with the compound was also noted In TABLE 5 are compared the average stool weights for each day during the medication periods In the preceding control days the average weight of the stools was 162 gm per day On institution of methylcellulose medication the weight dropped to below normal the first day and then gradually increased until the new higher level of 207 gm was attained on the third day With the compound tablets in either dosage this preliminary constipative action was apparently lacking The new level of stool output seemed to be established even on the first day of medication, thus giving the patients immediate tangible evidence of the effectiveness of the new therapeutic regimen

From these studies it appears that the combination 0 4 gm methylcellulose—0 1 gm psyllium tablets have substantially more bulk laxative effect per tablet than plain methylcellulose tablets It is also apparent that the compound tablet produces its increased bulk of stool more promptly than the plain methylcellulose tablet The addition of psyllium to the methylcellulose therefore appears to provide a combination bulk laxative with enhanced therapeutic value

TABLE 5

AVERAGE WET WEIGHTS IN GRAMS DURING EACH DAY OF THE MEDICATION PERIODS

Day	Methylcellulose tablet	Compound tablet	
	9 tablets per day	6 tablets per day	9 tablets per day
1st	132	181	210
2nd	175	169	214
3rd	207	161	204
4th	188	223	220
5th	230	180	253
6th	197	175	195
7th	204	197	196

DOCTOR TAINTER I have broken down the water intake in previous studies but not in the last methylcellulose study There has been no difference that I could detect. Obviously, if a person were to drench himself with water by drinking a gallon or half a gallon extra a day, he might conceivably have a more moist stool The water content in any one individual however, is a very stable figure A difference of only one or two per cent in the water content makes a difference between having a fairly firm stool and having a liquid stool Apparently a colloidal system in which the water content is very critical is involved and you get a large change in consistency with a small degree of change of water

QUESTION Does the sodium remain bound and pass through without being absorbed?

DOCTOR TAINTER I assume you mean the sodium of the sodium carboxy methylcellulose I know of no studies on this point If the sodium were ionized and absorbed, the carboxymethylcellulose radical would have to be combined and excreted in combination with some other positively-charged ion such as potassium calcium magnesium *etc*

QUESTION That might perhaps be of some importance in cardiacs?

DOCTOR TAINTER I think you might make a story for the use of magnesium carboxymethylcellulose or the calcium or even the ammonium salt if that were chemically feasible to avoid sodium intake In the cardiac you could eliminate the possibility of sodium intake much more easily by using methyl cellulose instead of sodium carboxymethylcellulose

QUESTION Were any *in vitro* tests made with methylcellulose with synthetic stomach juice? How did you get it into solution in the ordinary room temperature or did you change the temperature?

DOCTOR TAINTER To get the material into solution in these tests of swelling capacity I placed the material in a large cylinder added the water on top of it and allowed it to swell to its maximum by letting it stand until we had a constant volume If you stir the material you will get a complete dispersion of the methylcellulose throughout the water and have simply a dilute solution of it It appears to dissolve whereas the karayas swell and persist as discrete particles The swelling of the methylcellulose is less affected by alkalinity and acidity than is that of the vegetable gums There is only a very small change in the amount of swelling a matter of 10 per cent in one half per cent hydrochloric acid or one per cent in sodium bicarbonate from the swelling in distilled water

DOCTOR QUIGLEY In the case of the bland compounds do you anticipate that the action in promoting bowel evacuation is any different from the same bulk with water in the colon from the bulk that would be held by the bland preparation that you are employing? Is it simply a case of bulk or has the preparation that you are employing any additional action?

DOCTOR TAINTER I have always assumed that we were dealing here with a bulk effect or distention but that is an assumption for which I have no evidence These materials have no chemical irritating power that I have ever seen or recognized There is no question that if you distend the gut by doubling the bulk of the stool as we have done in some of these experiments you have to have an increase in the number of defecations or an increase in the size of the

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Discussion of the Paper

QUESTION Do you control the water intake in these patients Doctor Tainter? Is there any influence on the water intake compared to the wet weight?

CLINICAL COMPARISON OF BULK AND STIMULANT LAXATIVES

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In view of the considerable discussion regarding the effect of bulk laxatives in comparison with the stimulant varieties it is surprising how few controlled experimental observations have been carried out in this field Direct psychologically sound scientifically planned tests of the clinical differences of these laxatives are rare

A study by McGuigan, Steigmann and Dyniewicz[1] on the various laxative dosages covered karaya gum bran cascara sagrada magnesium sulfate and phenolphthalein but these authors failed to compare the drug in the same group of patients or to compare their clinical effectiveness

In a previous study Cass and Wolf[2] observed the effects of methylcellulose and psyllium on patients who had been receiving liquid milk of magnesia fluid extract of cascara sagrada or mineral oil A control period on the usual laxative was compared with a period on the new medication Since however the patients knew what they were receiving a valid criticism may be made here and it is difficult to gauge precisely the subjective factors in such a survey

The present study has eliminated this objection by the use of a rigidly controlled blind clinical trial in which neither the observer nor the patient knew the identity of the medication or that one of the medicines was a placebo

Method The composition and amount of the medications under test are presented in TABLE 1 In essence the medications consisted of lactose methyl cellulose and caroid and bile salts with phenolphthalein all in the form of identical tablets both with regard to external appearance and by reference to the taste and appearance when broken The total daily dose of methylelclulose amounted to 4 0 gm equivalent to or slightly more than the usually recommended dose The total daily dose of caroid and bile salts with phenolphthalein equaled four tablets of the commercial product which is the manufacturer s recommended dose To maintain the blind test conditions this medication was given in eight one half strength tablets

The studies were carried out at the Long Island Hospital Boston Mass a chronic disease hospital with approximately 1200 patients All of the patients under observation were semiambulatory (bed or chair) permanently institutionalized and severely constipated

Medications were administered by a technician and the observations were made by a full time nurse neither of whom knew the code All patients received all three medications The sequence in which the medications were given however was randomized The observations were obtained daily by the nurse from the floor nurses notes and the patients responses to questions as demonstrated in TABLE 2

Observations comprised

(1) Frequency of stool
(2) Consistency

stools I do not know whether there is some irritation that adds to that or stimulates action beyond the mechanical effect

Doctor Quigley Instead of stimulating, it might be the soothing action beyond the soothing effect which water would have

Doctor Tainter That is a very interesting suggestion For example, in ulcerative colitis or mucous colitis where a demulcent action might be beneficial, it might overcome any irritation that is there It is entirely conceivable that methylcellulose or psyllium would have demulcent and soothing actions which would decrease irritation, but I do not know of any quantitative studies of the use of these products in ulcerative colitis It may be that some other clinicians have observations on this that would be very interesting

Doctor Ingelfinger Have any studies been carried out where methyl cellulose suspensions or dispersons have been put in the human colons to see what their water retaining capability is, as opposed to the water absorption function of the human colon?

Doctor Tainter I don t know of any fistula studies They would be rather difficult to carry out, because the water uptake under those conditions is relatively slow *You would have trouble holding the material in the colon* long enough to make a good quantitative estimate of the changes It would be my guess that most of the swelling takes place in the small intestine where you have a much higher fluid content and that there is some dehydration and desiccation of the material in the colon just as there is of other fecal contents

TABLE 2
INTERVIEW CARD

Name__________ Number__________ Medication No.__________

Ward__________ Age__________ Sex__________ Activity

Bed	Wheel chair	Ambulatory

Day		1		3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Date																																
B M	0																															
	1																															
	2																															
	3																															
	3+																															
Consistency	Watery																															
	Soft																															
	Hard																															
Some effects	Gas																															
	Cramps																															
	Fullness																															
	Nausea																															
	Other																															
Well being	Good																															
	Fair																															
	Poor																															

Graded 1 watery
2 normal
3 hard

(3) Side-effects
Nausea, vomiting, cramps, distention, tenesmus
(4) Number of enemas required
(5) Alteration in dosage schedule

If a patient had no bowel movement for three days an enema was administered in the afternoon on the third day Medication was continued regardless of the administration of enemas, and no laxative medication was given other than that employed in the study Each medication was given for 10 days and then the patient was immediately changed to the next medication for a 10-day period The study lasted 30 days in all, 52 patients completing the entire series and receiving each of the three medications

Results The data are presented in TABLE 3 *Column 1* refers to the types of medication Note that the three medications were not given in this sequence however, but were purposely administered at random *Column 2* relates to the number of patients All 52 received each type of treatment, for 10 days each per medication given *Column 3A* presents the average number of bowel movements per 10 day period per patient for each of the three medications Because of the necessity of giving enemas the number of which is shown in *Column 5*, the mean values for methylcellulose and lactose in *Column 3A* are augmented by these figures

Column 3B shows the average number of *spontaneous* bowel movements per patient per 10 day period which is somewhat lower than the enema augmented figures in *Column 3A* It will be noted that lactose produced a spontaneous frequency of 2 7 bowel movements per patient per 10 days, or less than 1 bowel movement per 3 days This established a most satisfactory state of constipation in the patients of the test group who required 46 enemas during the lactose period

TABLE 1
MEDICATIONS

	C mpos tio p T bl t		D e
Caroid & bile salts with phenolphthalein (half strength)	Bile salts compound	0 036 gm	4 tablets morning and evening
	Ext cascara sagrada	0 024 gm	
	Phenolphthalein	0 016 gm	
	Ext nux vomica	0 002 gm	
	Capsicum	0 003 gm	
	Papain (caroid)	0 040 gm	
	Milk sugar starch and magnesium stearate	0 479 gm	
Methyl cellulose	Methyl cellulose	0 500 gm	4 tablets as above
	Starch quassin talcum nuchar methyl salicylate FD&C yellow No 4	0 008 gm	
Placebo	Milk sugar	0 400 gm	4 tablets as above
	Starch quassin talcum nuchar methyl salicylate FD&C yellow No 4	0 105 gm	

On the caroid and bile salts with phenolphthalein, no side-effects were observed There were no complaints of nausea vomiting cramps distention or tenesmus even when an excessive bowel action was present In this type of group where constipation is so ingrained, relief is the criterion and with a blind technique we had no choice but to wait for changes before altering the dose In addition there were no complaints of obstipation and it has been noted that 24 patients actually had to omit one or more doses Five patients had to omit two successive doses because of a somewhat excessive laxative effect

One thoroughly practical objection of the patients not quantitatively recorded as a side-effect however was the necessity for taking eight tablets a day throughout the experiment The patients resented severely this arduous task and a firm hand was necessary in maintaining the tablet intake at the eight a day level Since the technique of the blind study requires that all medication regimens must be similar in our experiment this meant that the fault of the bulk laxative had to be extended to all This excessive number of tablets would not ordinarily be required if full strength caroid and bile salts were used

The bowel content modification of the bulk laxative is adequate which we have found to be true of other laxatives of the same general type Without some stimulation, however mechanical removal of the stool may be required by enema and is further necessitated by the delay in onset of the bulk laxative effect The patients antagonism to large doses of medication without results *to show for their cooperation (already noted in the placebo period) is also* present in the methylcellulose period but is somewhat overcompensated in the caroid and bile period From a purely practical viewpoint a stimulant laxative is accordingly necessary except for rare contraindications

The essence of the use of a stimulant laxative is its anticipation of an adequate bowel habit Some stimulation is often necessary and the stimulant laxative alone can expeditiously and conveniently perform the operation

Discussion It is clear that the patients in this study were so severely constipated that they had an average frequency of one bowel movement every third day Further it is quite apparent that they were very uncomfortable and suffered side effects while they were on the placebo The patients benefited greatly from the use of either of the laxatives

It has been stated that bulk laxatives are preferable to stimulant laxatives in the aged or institutionalized patient The following reasons are usually given.

(1) This type of patient suffers from constipation because of *insufficient* bulk in his diet By giving a bulk laxative the physician is restoring to normal the gastrointestinal tract

(2) The normal stimulus to defecation is increased bulk in the lumen of the colon A bulk laxative acts through this normal mechanism

(3) Bulk laxatives are harmless and no dependence or tolerance results from their use

In contrast to the foregoing the following advantages of the stimulant laxatives should be noted

(1) The stimulant laxatives effectively increase muscular activity of the large

TABLE 3
RESULTS

1	2	3 A	3 B	4	5	6	7
Treatment	Number of patients	Bowel movements per 10 days		Total dosage per patient	Total number of enemas	Number of patients with reduced dosage	Average consistency
		Including enema	Excluding enema				
Methylcellulose	52	7 865	7 808	80	3	0	2 01
Lactose	52	3 615	2 731	80	46	0	2 57
Caroid and bile	52	13 519	13 519	69 8	0	24	1 89

Methylcellulose gave a frequency of 7 8 bowel movements per patient per 10 days This is approximately one bowel movement a day for 8 days out of 10 Only 3 enemas were required for the group as a whole during the methyl cellulose period

Caroid and bile salts with phenolphthalein produced a frequency of 13 8 movements per patient per 10 days, or 3 bowel movements more than the basic one a day rate for the caroid and bile period No enemas were required during this caroid and bile medication

Column 6 shows the number of patients given reduced dosages of the medications Occasionally the dose of caroid and bile salts produced an excess laxative effect Whenever two bowel movements took place between the morning and evening standing orders were in effect that no matter what the medication the evening dosage (four tablets) was to be omitted Continuation of laxative treatment was necessarily contraindicated under such circumstances The decreased number of administrations of caroid and bile salts represents 24 patients who did not receive the full dosage of medication The final analysis showed that only in the case of caroid and bile treatment was this necessary

Column 7 provides a numerical summary of the consistency data For ease in establishing a standard of comparative analysis a hard bowel movement was assigned a score of 3 a medium movement a score of 2 and a soft movement a score of 1 By means of this scoring system a statistical mean consistency was obtained for all of the medications Methylcellulose gave a value of 2 01 connoting that the stool consistency averaged medium for all the subjects while they were on this medication Lactose resulted in a value of 2 57 which is significantly different from the 2 01 of methylcellulose and indicates a fairly high percentage of hard movements Our test group was accordingly constipated in all respects Patients who received caroid and bile salts with phenolphthalein showed a value of 1 89 which likewise is clinically different from 2 01 and indicates an increased number of soft movements in this group

The side effects on which the patients were regularly questioned were nausea vomiting cramps, distention and tenesmus However the patients were not backward in volunteering information concerning headaches and obstipation Most of these effects occurred with the placebo Nonetheless five patients receiving methylcellulose complained of cramps and three of persistent constipation, which required enemas as shown in TABLE 3

that senna and cascara sagrada may be taken steadily for 50 years effecting either no change or only mild changes in bowel habits[19] dependence would appear to be relatively unlikely Tolerance might be inferred if on taking these patients off laxatives they continued to have movements at their usual rate However, one would have to be certain that the same thing would not have happened whenever the patient started taking laxatives In short one would have to be sure that the dose of laxative that the patient was taking had *not been a placebo all along*[15] *There would accordingly appear to be little* concrete evidence for making the choice of a bulk or a stimulant laxative on the basis of irritation dependence or tolerance

The foregoing discussion does not carry the implication that there is no place for bulk laxatives in the management of constipation Indeed our studies have shown that a bulk laxative may be quite effective It is our impression, however that the stimulant laxatives have a slight advantage over the bulk ones particularly for the purpose under discussion the regulation of chronic aged or institutionalized patients

In the preceding part of this report a basic point of philosophy has been assumed which might bear a more explicit discussion our conviction that laxatives have a place in the management of constipation Some physicians deny the usefulness of laxatives They quote examples of patients with Hirschsprung s disease to indicate that no harm ensues from allowing feces to remain in the colon for a month or two However a patient with Hirschsprung s disease has gradually become accustomed to having a dilated bowel A person with the habit of moving his bowel once a day will become quite uncomfortable after three or four days without a movent and by the end of nine or ten days he will begin to show signs of intestinal obstruction

The patient who fails to have regular movements and yet cannot be regulated by diet, exercise and psychotherapy deserves laxative therapy Stimulant laxatives would appear to be preferable in that they need not be given continuously but only as the need arises Moreover gradual reduction in dosage of stimulant laxatives has been shown to be an effective way to cure constipation All long term laxative therapy should be under the supervision of a physician for proper regulation and the prevention of abuse No laxative is completely harmless and excessive use may result in severe electrolyte depletion, as has recently been demonstrated by Schwartz and Relman [20]

Conclusions

(1) In a blind controlled study it was demonstrated that either 4 0 gm. (eight tablets) of methylcellulose or four tablets per day of caroid and bile salts with phenolphthalein produced a significant and adequate laxative effect

(2) Caroid and bile salts with phenolphthalein produced a more rapid onset of laxative action than methylcellulose

(3) Methylcellulose requires the administration of eight tablets daily and this large number of tablets was resented by the patients

(4) Caroid and bile salts with phenolphthalein proved more uniformly effective than methylcellulose and produced fewer side-effects

colon The constipated aged or institutionalized patients eat the same diet as the nonconstipated The defect, in some of the patients at least, would appear to be in the reactivity of the intestinal musculature As Portis and King[3] have stated in the March 1952 issue of the *Journal of American Medical Association* "Many physicians have approached this problem in the past from the stand point of producing great bulk However, it seems logical that, if the muscle could be effectively stimulated pharmacologically, evacuation of the bowel would be more regular" Portis and King used neostigmine

However, Straub and Triendle in 1934 and 1937[4, 5] demonstrated that senna was a *specific stimulant to the musculature of the large colon of the cat* Presumably, the same holds for all of the anthraquinone laxatives, including cascara sagrada The caroid and bile salts with phenolphthalein as used in this study, may probably also be classed in the same category of pharmacologically specific, efficient, direct stimulants of intestinal musculature

The illogic of always using bulk laxatives in the treatment of constipation has been colorfully described by Alvarez[6] 'As I often say, the normal colon is like a railroad siding with three box cars on it Every day, one comes down and bumps another off the lower end, so that three remain In these constipated persons a car gets bumped off the lower end but always some ten cars remain on the siding

A muscle stimulant would seem preferable to bump along the box cars in this type of patient, who is in need of power rather than bulk

(2) There is no danger from impaction or esophageal obstruction in using the stimulant laxatives In the case of bulk laxatives on the other hand, copious quantities of water are recommended Belmont,[2] in the *Journal of the American Medical Association* in 1952 has reported a case of a 67 year-old man who incurred an esophageal obstruction requiring endoscopic removal owing to the ingestion of three methyl cellulose tablets The stimulant laxatives are able to withdraw water from the bodily stores and their action is thus exerted independently of the ingestion of water In heart failure nephritis *etc* removal of water via the gastrointestinal tract may be quite beneficial

(3) There is very little evidence that the stimulant laxatives cause colitis, dependence, or tolerance Certainly senna cascara sagrada, and phenolphthalein are not irritants When placed in contact with isolated intestinal loops, or with the skin or mucous membranes they cause no inflammation, edema, leucocytic infiltration or hyperemia[8, 9, 10, 11] When given in excess quantities to the intact animal they may cause increased mucus production in the colon but anything which causes an excess number of bowel movements will increase mucus production as witness nervous tension On this score, the increased mucus production is hardly a significant sign of irritation or inflammation[12, 13]

The occurrence of dependence or tolerance is a very difficult factor to determine No studies of sufficiently long duration have been undertaken to settle this point in one way or the other Tolerance has been claimed to develop as an effect of both the stimulant and the bulk laxatives[15, 16] Other workers in this field have claimed that tolerance does *not* develop[17, 18] In view of the fact

ANTISPASMODIC THERAPY FOR THE HYPERACTIVE COLON

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The administration of spasmolytic drugs is but a small and perhaps not even essential part of the clinical approach to antispasmodic therapy for the hyper active colon Indeed the term antispasmodic although generally used is unfortunate, in that it implies that colonic muscular spasm *per se* adequately accounts for the pain and disturbed proficiency of elimination characteristic of bowel dysfunction This is recognized as an oversimplification The concept of bowel dyssynergia and dyskinesia[1,2,3,4] is better supported by experi mental and clinical observation and more adequately explains the phenomena associated with colonic disorders Variable intersegmental imbalances in co lonic tone and in propulsive and nonpropulsive motility have been shown to be concerned in the production of pain and of constipation and diarrhea In simpler terms resisted contraction and blocked propulsion may be said to underlie pain and constipation while propulsive motility which is excessive or which is inadequately blocked results in diarrhea

A beginning has been made in the correlation of disturbed motility patterns with clinical syndromes It has been shown that under appropriate stress colonic motility may increase in normal individuals as well as in those with spastic colon[5,6,7,8,9] In ulcerative colitis total colonic muscular action may actually be reduced but becomes more propulsive in type[10,11] Diminished rhythmic contractions in the distal colon accompanied by heightened activity in the proximal colon may be the dynamic basis for diarrhea[12] In constipation there may be increased nonpropulsive activity of the sigmoid with a hypody namic proximal colon[9,13] The motility relationships of various colonic segments, as well as secretion and vascularity are modified by local disease or by chemical hormonal and neurogenic stimuli of extracolonic origin The importance of stress and mood has been well demonstrated It must be confessed too that there is great variability of individual symptomatic response with apparently similar colonic motility patterns These differences in neuro or psycho sen sitivity *are poorly understood but are clinically important*

If the dystonic colon be defined broadly as one which responds in a faulty manner to stimuli the hyperactive colon may be considered as a variant in which there is general or segmental colonic overaction Pain disturbances of bowel evacuation and oversecretion of mucus are the major clinical manifes *tations*[14] In any group of patients having evidence of colonic dystonia the majority will be concluded to have no demonstrable organic basis and in most of these the evidence will suggest an underlying anxiety state In a significant proportion however local and extracolonic etiologic factors of non psychogenic nature may be involved (TABLE 1) The irritable colon syndrome may accord ingly be observed in the milder forms of amebiasis[15] in polyposis and accom panying recurrent minor episodes of diverticulitis A not infrequent cause is food allergy the most common offenders in this regard being milk wheat egg

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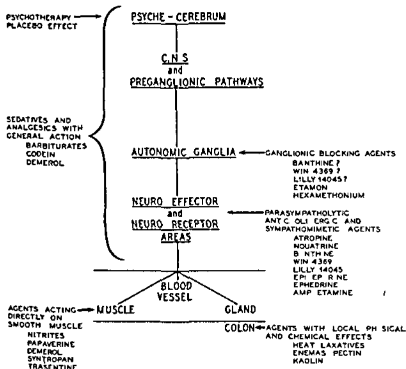


FIGURE 1

sufficiently severe and deep-seated to require the more expert help of the trained psychiatrist

Therapy with diet and medication must be looked upon as more or less necessary adjuncts to management which primarily attempts to control or modify the etiologic factors already mentioned Where there is any suspicion of a specific food allergy a simple primary diet consisting of several rarely allergenic foods may be given To this regimen are added representatives of the major food classes one by one at intervals of several days When any added food cau es a significant exacerbation or recurrence of symptoms of bowel dystonia it is withdrawn and its etiologic significance further assessed at a later time after the attainment of an adequate diet consisting of foods which cause no difficulty Aside from the exclusion of specific allergies however all patients having hyperactive bowels are benefited by the use for a period of time of bland diets which omit foods that chemically physically or reflexly precipitate colonic over action or distress In such a diet very cold or iced foods the so called ga

TABLE 1
200 PATIENTS HAVING COLONIC DYSTONIA*

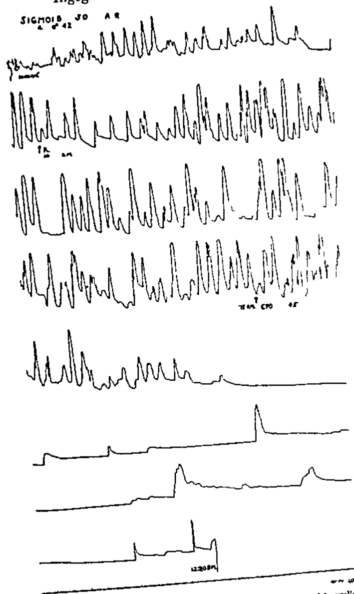
Organic	
Food allergy	14
Laxative abuse	12
Amebiasis	11
Diverticulosis with diverticulitis	8
Carcinoma of colon or rectum	6
Colonic polyps	3
Other infestations	3
Hyperthyroidism	2
	59
Nonorganic or Functional	
Spastic or Irritable colon (High incidence of underlying anxiety)	141

* Evidence of colonic dysfunction more than 2 months without bleeding or significant systemic deterioration. Symptoms include abdominal cramps, diarrhea and/or constipation, abdominal unrest, excess mucus secretion.

the citrus fruits and tomato. Laxative abuse and a variety of parasitic infestations may be concerned and occasionally even carcinoma of the colon or rectum. No confusion will arise of course from such frank causes of bowel hyperactivity as ulcerative colitis of specific and nonspecific type, and from the usual instances of neoplasm in which bleeding or obstructive symptoms are prominent.

The final common path for stimuli to affect the colon resides in the autonomic nervous system and the neuro-effector junction in the bowel. The disturbed function of the hyperactive colon may be allayed by measures directed toward any portion of the pathways or structures involved in the mediation or production of its manifestations (FIGURE 1). Thus strictly speaking, any treatment from psychotherapy down may properly be referred to as "antispasmodic" therapy if it modifies for the better the pattern of faulty colonic response.

In the management of the hyperactive bowel, the first critical step is to determine the etiologic factors concerned. The appropriate specific treatment of any local or systemic causative agent will relieve the hyperactive state. Since the finding of specific etiologic factors involves a thorough study of the patient and his gastrointestinal tract this procedure is in itself a major therapeutic measure in the larger group of patients with hyperactive colons finally concluded to be on a "functional" or "psychogenic" basis. An aggravating factor in such patients is their conviction that serious organic disease is concerned. When on the basis of careful evaluation one can reassure them of the absence of any demonstrable organic lesion a significant source of tension is removed. This, together with an explanation in simple terms of how nervous stresses acting through the autonomic system may cause disturbance of bowel function is sufficient in many milder cases to relieve the evidence of bowel hyperaction. This is etiologic therapy for the hyperactive colon in the same sense as specific drug treatment for a causative amebiasis or specific diet control when a food allergy is concerned. Fortunately in any large group of sufferers from bowel dystonia of psychogenic type relatively few have neuropsychiatric disturbances



F cuʀᴇ 3 Effect f compound 14045 (El lf t 1 cy l h xyl-1 phenyl-3 pyrollidine-1 p pa 1 m thobromide) on motil ty patt rn f igm d N t marked ppres ff t f 100 mg t k rally Th w plac bo fl t w th lactos tabl t

formers, strongly laxative foods, and those with an excessive residue after digestion will be omitted There is no great contradiction to the use of soft bulk or lubricant laxatives in the patient having a hyperactive colon but, obviously, laxatives with strong chemical or osmotic action should be avoided since they exaggerate bowel dystonia

The use of medication in the management of patients having hyperactive colons is predicated on drug action of both nonspecific and specific nature The giving of any medicine even one that is inert, may exert a so called 'placebo-effect" in allaying symptoms Objectively demonstrable inhibition of small bowel activity by placebos has been shown to occur[16] This is presumably a psychogenic effect which in practice would no doubt depend to a variable but significant degree upon the conviction and confidence manifested by the doctor in the efficacy of the medication given In other studies, there was no appreciable change in colonic function for variable periods after placebo administration,[9, 17] (FIGURES 2 and 3) The pharmacologic response to a given drug however, may be reinforced or counteracted by existing stimuli of other nature such as the feeling state of the subject during the period of study[8]

Sedatives and analgesics having general action, of which the barbiturates are the most widely used are rational adjuncts to the clinical management of hyperactive colonic states The effect of the barbiturates is primarily that of render

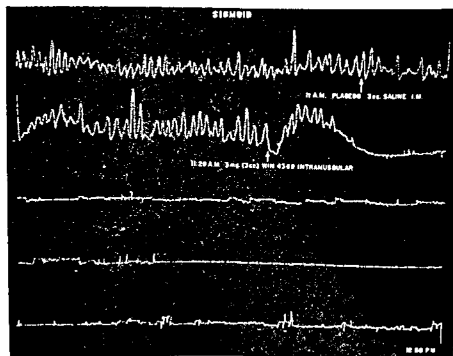


FIGURE 2 Eff t f compo d 4369 {M od l 2 D thylam oethyl 2 y l pe tyl 2 (2 th yl)hyd xy e- tat m th b mid l m t l ty patt rn f ugm d t m k d pp ff t f 3 mgm g tram c larly There w s n pl bo effect w th h

suing discomfort may be worse than the distress complained of originally Until by more precise studies we have available to us therapeutic agents specifically helpful in modifying motility patterns in a desired direction it must be recognized that antispasmodic therapy with such drugs is something of a hit-or miss proposition It has been pointed out there is as yet no real experimental evidence to indicate that hypermotility is affected more than normal motility by these agents[18] However the encouraging return to a more normal functional pattern in clinical cases of hyperactive colon suggests that such may nevertheless be a result of this therapy in the intact human The worth of any treatment of colonic dystonia must be finally assessed in the patient having symptoms although such evaluation is admittedly subject to considerable error The experimental demonstration of pharmacologic effect on the colon of animals and even of humans is no guarantee of efficacy in clinical practice

In the management of patients affected by severe abdominal cramps and diarrhea in ulcerative colitis and of patients having severe cramps of spastic colon accompanied by diarrhea or not, the following preparations parenterally administered are usually promptly effective in affording moderate to complete relief especially of cramps although this relief is often transient and the dosage must be repeated

(1) Atropine sulfate—0 6 to 0 8 mgm —subcutaneously given in severe cases this drug affords excellent symptomatic relief lasting from one half an hour to several hours and is given every four to six hours It is best given only to patients whose condition is severe enough to require confinement to bed Distress owing to the associated effects of xerostomia blurring of vision rapid pulse and nervous excitation is rendered more tolerable by the simultaneous administration of a barbiturate such as sodium phenobarbital in dosage of 60 to 120 mgm While the latter has no direct antispasmodic action its sedative effect is probably beneficial in suppressing perception of distressing symptoms and in diminishing excitor stimuli to the colon of central origin The experimental inhibition of colonic motility by atropine given parenterally has been demonstrated by some[19, 27] although other reports are less favorable[9, 24, 25]

(2) Demerol in 100 mgm dosage may be given under similar circumstances with excellent relief It has both an analgesic and antispasmodic action and is mildly sedative[3] Obviously the danger of habituation limits its use The prolonged use of Demerol codeine or morphine by mouth or parenterally can only be condemned

(3) Papaverine hydrochloride given intravenously in the bed patient in doses of 60-120 mgm will often produce dramatic relief of severe abdominal cramps caused by hyperactive colon The effectiveness of this drug depends on its ability to decrease tone of all smooth muscle including the sphincters[3] When given intravenously its suppressive effect on intestinal motility is quite transient in the experimental man and animal Yet in actual clinical use the effect may be prolonged for several hours It has no habit forming tendencies even though listed as a narcotic

(4) Transentine in 50 mgm dosage intramuscularly may be effective in the circumstances under consideration although its worth is questionable Favorable experimental results have been reported[19]

ing the patient less sensitive to both his internal and external environment. Dosages in the therapeutic range exert no apparent specific pharmacologic effect on bowel activity,[18] but there is certainly a lessening of the patient's central awareness of his bowel distress and, possibly, an actual diminution of the intensity of the stimuli arising from the dystonic colon. Since barbiturates help to allay psychologic tensions, their administration over a period of time serves to diminish excitor stimuli of central origin. In this sense, therefore, such drugs are also "antispasmodic." One might speak of psychotherapy, placebo effect, and sedative analgesic therapy as centrally acting antispasmodic measures. Preparations containing kaolin and pectins and lubricant and soft bulk laxatives, to the extent that they allay bowel hyperactivity by a local soothing physical action, may also be properly considered as antispasmodic. The application of heat to the abdomen is certainly a measure clinically helpful in relieving the pain of colonic dystonia, perhaps by a reflex inhibition of colonic motility.

Those drugs which are commonly referred to as "antispasmodics" exert a specific pharmacologic effect in suppressing propulsive and nonpropulsive bowel contractions and diminishing bowel tonus. They are given in the hope that inhibition of bowel activity or overactivity, particularly that of smooth muscle, lessens or eliminates the immediate cause of painful stimuli and of disturbed elimination. This use of antispasmodic drugs is a form of specific symptomatic therapy. The drugs exert their major effects peripherally on one or more segments of the neuromuscular structures concerned (FIGURE 1). Recent experimental and clinical studies permit of some evaluation of the actual or potential usefulness of a number of these agents (TABLE 2). The presently available antispasmodic agents known to have definite pharmacologic and therapeutic effects tend to reduce or abolish overall colonic motor activity. It is quite unlikely that too marked or complete inhibition of bowel activity would ever be therapeutically indicated. On occasion, strong anticholinergic agents may cause such hypotonia, hypomotility, and distension in the patient that the en-

TABLE 2

ANTISPASMODIC DRUGS FOR THE HYPERACTIVE COLON

I *For Parenteral Use*	
(1) Atropine sulfate	0.6–0.8 mgm. s.c. or i.m.
(2) Demerol	100 mgm. i.m.
(3) Papaverine	60–120 mgm. i.v.
(4) Nitroglycerin	0.6 mgm. sublingually
(5) Trasentine	50 mgm. i.m.
II *For Oral Use*	
(1) Atropine sulfate	0.6 mgm.
(2) Tincture belladonna	10–20 minims
(3) Novatrine	5 mgm.
(4) Banthine	25–50 mgm.
(5) Trasentine	75 mgm.
(6) Syntropan	50–100 gm.
(7) Experimental drugs	
(a) Compound 4369 (Monodral, 2-Diethylaminoethyl 2-cyclopentyl-2-(2-thienyl) hydroxyacetate methobromide) 2.5–5 mgm.	
(b) Compound 14045 (elorine sulfate, 1-cyclohexyl-1-phenyl-3-pyrollidine-1-propanol methobromide) 50–100 mgm.	

many more fundamental observations must be made before therapy can be more logically evaluated

The adrenergic and sympathomimetic drugs (epinephrine ephedrine, amphetamine) have been shown to exert an appreciable inhibitory effect on gastrointestinal motility [5, 11, 27, 8] However their cardioaccelerator and vasopressor actions prohibit their practical clinical use as antispasmodic agents in colonic dysfunction

Etamon and hexamethonium have strong blocking effects on both parasympathetic and sympathetic ganglia especially the latter and a striking inhibition of intestinal smooth muscle activity can be demonstrated by means of them [18, 29, 30, 31, 32] Their hypotensive effects relegate against their usefulness in the management of colonic disorders The other agents listed in the ganglionic blocking group in dosages employed clinically exert their major effects as parasympatholytic and/or anticholinergic agents and not as ganglion blocking drugs

The anticholinergic group of antispasmodic drugs of which atropine is the prime example has thus far proved to be the most useful in the clinical management of colonic dystonia, and synthetic preparations of this class are beginning to appear in overwhelming profusion

Banthine has been shown to bring about striking and prolonged inhibition of colonic motility when given orally in 25 to 100 mgm. dosage [15] I have found it clinically effective in doses of 25 to 50 mgm given four times daily It is helpful in relieving abdominal cramps and in lessening diarrhea in patients having an irritable colon and occasionally in ulcerative colitis Larger doses should not be used since they exaggerate the associated mouth dryness and tendency to blurring and may cause considerable abdominal distension or constipation These latter discomforts induced by the drug are no more appreciated than the cramps and diarrhea which they replace

Two new anticholinergic drugs which have potential therapeutic value in hyperactive colonic states may also be mentioned They have received some preliminary study in the Gastrointestinal Research Unit of the Long Island College Hospital The first of these compound 4369 [Monodral 2 Diethylaminoethyl 2-cyclopentyl 2-(2 thienyl)hydroxyacetate methobromide] has both antisecretory and motorsuppressive effects experimentally in both animals and humans [33] In the human oral doses of 5 to 20 mgm consistently depress gastric and small intestinal motor activity as shown by balloon kymographic and radiographic method While no effect on sigmoid motility could be shown when 5 to 40 mgm were given by mouth there was nevertheless striking inhibition with as little as 2 or 3 mgm given intramuscularly (FIGURE 2)

The drug has been tried clinically in 29 patients with irritable or spastic colon It was given orally in dosages of 10 to 60 mgm daily There was good to excellent relief of cramps diarrhea abdominal rumbling and excess mucus secretion in 23 of the 29 cases The drug was also somewhat helpful in 3 of 5 patients having ulcerative colitis

Another drug compound 14045 (1 cyclohexyl 1 phenyl 3 pyrollidine 1 propanol methobromide) has been found by us to suppress strikingly antral duo-

(5) Amyl nitrite inhalation and nitroglycerin 0 6 mgm sublingually will often relieve the pain of colonic dystonia promptly The action of amyl nitrite however, lasts only a few minutes and its usefulness is limited by the associated flushing, headache and palpitation Nitroglycerin under the tongue has a more prolonged action and the side effects are tolerable It can be used several times daily with relatively satisfactory relief of cramps Nitrites have been shown to decrease colonic tone and/or contractions under experimental conditions in man [19]

In the ambulatory or bed patient subject to recurrent cramps, abdominal distress and diarrhea of milder severity, oral use of the belladonna alkaloids have long been known to be helpful clinically The results of experimental trial in humans by balloon kymographic methods have not been entirely consistent Good[19, 0] and poor[9, 25] results have been reported Clinical evaluation is complicated also by the fact that the drugs are almost invariably given with an accompanying sedative There is nevertheless little doubt that atropine sulfate in 0 6 mgm dosage or tincture of belladonna in doses of 10–20 minims, given several times daily with or without an accompanying sedative quite effectively allay abdominal distress and may diminish diarrhea in colonic dystonia

Novatrine (homatropine methylbromide) is less effective than atropine in blocking peripheral vagal impulses [23] It has been shown to possess spasmolytic properties when given to humans parenterally [26] However its experimental efficacy in humans given the drug orally has been slight[9] or poor [18] Its side effects are practically nil I have used this drug clinically to a rather extensive extent in 5 mgm dosage four to six times daily with excellent relief of the milder symptoms of hyperactive colon Novatrine is one of these drugs having a clinical usefulness apparently out of proportion to its objectively demonstrable value under experimental conditions

Trasentine 75 mgm and syntropan, 50–100 mgm , have not been clinically effective in my experience While there have been reports of successful experimental inhibition of colonic motility in humans following the use of these drugs when parenterally given [19] they have been found generally ineffective in recommended oral dosage [9, 18, 25] The natural tendency is to discount clinical reports of efficacy in the face of negative experimental experience The psychotherapeutic effects of any drug administration under inadequately controlled clinical conditions may lead to erroneous conclusions Yet it should also be kept in mind that the experimental testing of these drugs has been quite limited as to number of subjects and as to area of colon under study The fact that no alteration of sigmoid motility can be demonstrated for example would not exclude the possibility of an effect on the proximal colon It is entirely possible too, that disturbances of small intestinal motility are also concerned in syndromes interpreted clinically as owing to colonic dystonia and drug action in this area could be clinically helpful and yet not be demonstrated in colonic motility studies Actually in spite of the increasing number of worth while balloon kymographic, and radiographic studies of the motility of various gastrointestinal segments under more or less controlled experimental conditions,

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denal, and sigmoidal motor activity when given orally in 100 mgm dosage[34] Its effect on the colon is illustrated in FIGURE 3 Others are stated to have obtained similar results by means of this drug[35] Clinical experience with this preparation in colonic dysfunction is insufficient at present, but it may be anticipated that its oral effectiveness and minimal side-effects will enable it to earn some place for itself in the therapy of colonic dystonia

A final word should be said about the use of antispasmodic agents in the patient having colonic dystonia in whom constipation is an outstanding complaint for these drugs by suppressing overall colonic motility, necessarily tend to have a constipating effect However, considerations which ascribe the constipation in such patients to bowel dyssynergia and the presence of nonpropulsive muscular hyperactivity in the distal portions of the bowel suggest that any agent which effectively inhibits this hyperactivity would tend to relieve the constipation In actual practice such is indeed the case These drugs especially when given in the smaller doses in conjunction with proper dietary control and the hydrophilic bulk laxatives often relieve not only the abdominal cramps but the constipation as well

In summary then, it may be said that antispasmodic therapy is a misnomer in that it implies that colonic spasm is of cardinal importance in the hyperactive colon The evidence indicates rather that complex disturbances of intersegmental motility relationships are concerned, *i e* dyssynergia and dyskinesia The use of spasmolytic drugs is only part of the clinical management of colonic dystonic states A firmer basis for the therapeutic use of these agents should be established by the experimental demonstration of a favorable modification of motility patterns specifically correlated with symptomatology of colonic origin Of even greater importance than spasmolytic drugs in so-called 'antispasmodic therapy are measures directed toward the discovery and removal or amelioration of those local and extracolonic factors organic or "functional' which result in bowel hyperaction

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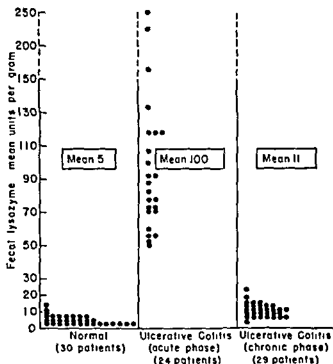


Figure 1

approximated 100 units per gram with a range of 49 to 250 units. This was in sharp contrast to the lysozyme titers observed in 29 patients in the chronic inactive or remission phase of the disease where a mean level of 11 units per gram was observed (FIGURE 1, TABLE 1). As the acute phase of the disease subsided the lysozyme titer fell concomitantly with the remission.

TABLE 1

FECAL LYSOZYME IN ULCERATIVE COLITIS DEMONSTRATING THE EFFECT OF HORMONE THERAPY IN REDUCING THE LYSOZYME TITER TO INACTIVE OR REMISSION LEVELS

	No. of cases	Mean lysozyme titer (units/gm)
Normal	30	5
Ulcerative colitis		
Active	24	100
Inactive or healed without hormone therapy	29	11
Ulcerative colitis†		
Before hormone therapy		133
After hormone therapy	7	16

Previously reported hormone therapy was administered.

† Present series of patients.

ANTILYSOZYME AND STEROID THERAPY IN ULCERATIVE COLITIS

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Lysozyme has been suggested as an etiological agent in the pathogenesis of chronic nonspecific ulcerative colitis because of the high lysozyme titer found in the stools and colonic mucosa of patients suffering from this disease It has been postulated that lysozyme removes the protective surface mucus from the colon and thus favors ulcerations of the denuded mucosa by proteolytic enzymes[1] The purpose of this presentation is to evaluate further the role of lysozyme in ulcerative colitis and to determine the effect of lysozyme inhibition upon the course of the disease process

Lysozyme is the name given by Fleming[2] to a mucolytic enzyme present in a number of tissues and secretions such as saliva tears, egg white, cartilage, and gastric juice It is also present in the mucosa of the stomach, duodenum, and colon and is found in normal feces Lysozyme has a molecular weight of about 18,000 and an iso electric point approximating 11 This enzyme hydrolyzes or depolymerizes a high polymer mucopolysaccharide It may be measured by the viscosimetric method of Meyer[3] using a mucopolysaccharide substrate prepared from the Micrococcus Lysodeikticus

Methods

The fecal lysozyme titer was determined in 30 normal subjects, 24 patients in the acute phase of ulcerative colitis and 29 patients in the chronic inactive healed phase The transition from the acute to the chronic stage of the disease was followed by serial analyses of the fecal lysozyme

Stools specimens were collected refrigerated as soon as possible, and then frozen until ready for analysis One gram of the well mixed stool was triturated with 10 cc of 0 1N HCl in the cold and the mixture was filtered The clear supernatant was then assayed by the viscosimetric method of Meyer[3] One unit of lysozyme was defined as the quantity which at 37 C and pH 5 3 reduced the viscosity of 0 4 per cent solution of the substrate to one half in ten minutes

Aerosol OT (di octyl sodium sulfo succinate) a detergent was administered orally in divided doses of 3 gm daily to patients having ulcerative colitis for periods of 12 to 66 days and the fecal lysozyme was measured at regular intervals

The effect of adrenocorticotrophic hormone and cortisone in therapeutic doses upon the fecal lysozyme titer was determined in another series of patients in the acute phase of the disease

Fecal Lysozyme Titer in Ulcerative Colitis

The fecal lysozyme titer appears to parallel the activity of the disease process During the acute phase of ulcerative colitis in 24 patients the mean titer

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TABLE 2

INHIBITION OF LYSOZYME BY AEROSOL OT

	Lysozyme activity before incubation with Aerosol OT		Lysozyme activity after incubation with Aerosol OT		Per cent inhibition of lysozyme
Lysozyme content of ulcerative colitis stool	481 units/gm				
1:330 dilution of stool + 4.0 mgm Aerosol OT	1.5 units/cc	2.0/cc	0 units/cc	0/cc	100%
1:330 dilution of stool + 0.4 mgm Aerosol OT	1.5 units/cc	2.0/cc	0.37 units/cc	0.5/cc	75%

incubated for 20 minutes at 37° C with 1 cc of a 1:330 dilution of stool extract from a patient with ulcerative colitis whose lysozyme titer was 481 units per gram of stool. The lysozyme activity was then determined in the usual way. There was complete inhibition of the lysozyme with 4 mgm of Aerosol OT (1 cc. of a 400 mgm per cent solution) and 75 per cent inhibition with 0.4 mgm (1 cc. of a 40 mgm per cent solution of the detergent) (TABLE 2).

The oral administration to patients of 1.0 gm of Aerosol OT three times daily in enteric coated capsules produced a prompt fall in the fecal lysozyme titer within 48 to 72 hours to normal levels or to lysozyme titers characteristic of the remission or chronic inactive phase of the disease (TABLE 1). This inhibition of fecal lysozyme activity by di-octyl sodium sulfo succinate was observed uniformly, the titers being diminished from pretreatment levels varying from 45 to 481 units per gram to posttreatment levels of 6 to 20 units per gram within two to three days of detergent administration.

The patients were maintained on detergent therapy (Aerosol OT) for periods of 12 to 66 days, during which the fecal lysozyme remained at low levels. After the detergent was discontinued, the lysozyme titer remained depressed for variable periods. The rebound to pretreatment levels occurred promptly in some instances (FIGURE 2) and required as long as 28 days in others (FIGURE 3, L.E., TABLE 3).

The prompt inhibition of fecal lysozyme by this detergent is demonstrated in FIGURE 2. The lysozyme titer fell from 131 units per gram to 13 units in 48 hours and remained below 20 units per gram for 36 days of Aerosol OT administration. When the detergent was discontinued, the fecal lysozyme rose to 101 units per gram within a few days. Upon resumption of detergent, the lysozyme titer again fell to levels of 20 units per gram or less and remained suppressed for the additional 30 days of Aerosol OT treatment.

There was no clinical evidence that the administration of this detergent and the consequent inhibition of fecal lysozyme altered the course of the disease process in any of the six patients, including the patient treated for a total of 66 days (TABLE 3 and FIGURE 2). There was no significant change in the proctoscopic appearance of the mucosa in these patients, and the stool guaiac, fever, white blood count or sedimentation rate did not improve more rapidly than would be anticipated from conservative medical management for an equal period of time without the detergent.

The close association between the activity of the disease and the lysozyme titer was observed in 11 patients in whom the transition from the acute to the chronic phase was followed by repeated lysozyme determinations over a period of one to eleven months The mean lysozyme titer was greatly elevated in this group during the acute phase with values of 57 to 321 units per gram As the disease passed into the chronic inactive phase, the fecal lysozyme titer gradually diminished to mean levels approximating 10 units per gram With a recrudescence of the disease or recurrence of an acute episode of ulcerative colitis the lysozyme titer again rose to previous levels approximating 110 to 130 units per gram [4]

The fecal lysozyme content of 30 normal subjects having no apparent gastrointestinal disease ranged from 3 to 10 units per gram with a mean titer of 5 units per gram (FIGURE 1) The daily variation in normal subjects on a regular diet did not exceed one unit Nonspecific diarrhea of bacterial or virus origin did not alter the lysozyme titer significantly The mean level in this group of 10 patients was 4 units per gram[5] (FIGURE 1)

Antilysozyme Therapy in Ulcerative Colitis

A number of antilysozyme agents have been used in the treatment of ulcerative colitis Encouraging clinical results have been reported in a limited number of patients treated with a 10 per cent suspension of nisulfazole 2 (p nitro benzene sulfonamide) thiazol [1] This preparation was found to inhibit lysozyme *in vitro* in a concentration of 20 mgm per cent (0007 molar)

The use of anionic detergents as inhibiting agents was suggested by the basic nature of egg white and mammalian lysozyme The most effective inhibitors reported were the normal alkyl sulfates of the series C_{10} to C_{18} [1] Sodium dodecyl sulfate, hexadecyl sulfate and octadecyl in concentrations of 0001 molar showed satisfactory lysozyme inhibition *in vitro* [1] It was found necessary however to increase the concentration of the nisulfazole and alkyl sulfates tenfold to inactivate the lysozyme content of human stools presumably because of the competitive action of the proteins in the stools for the inhibitors [1]

Sodium lauryl sulfate deacidite[6] (anion exchange resin) [6] dyes (Niagara sky blue and chlorazol fast pink) [7] ultraviolet light and light in the presence of riboflavin,[8] have been reported to inhibit lysozyme *in vitro* but clinical reports on their effectiveness in ulcerative colitis are not available

Enzyme Inhibition by Aerosol OT

In vitro inhibition studies in our laboratory with a large number of detergents and enzyme inactivators led us to the selection of Aerosol OT* as the most effective inhibitor of lysozyme [4]

Aerosol OT is a wetting agent belonging to a group of surface active substances which lower surface tension and interfacial tension Aerosol OT is di octyl sodium sulfo succinate (molecular weight 444) It is soluble in water and in most organic solvents oils and fats

One cc of an aqueous 400 mgm per cent solution of Aerosol OT (4 mgm) was

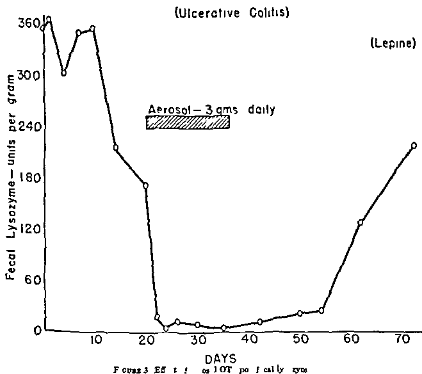
* The [illegible] tho[illegible] are grat[illegible]ful to Docto[illegible] B[illegible]nj[illegible]m[illegible] W Ca[illegible]y [illegible]f th[illegible] L[illegible]de[illegible]l Labo[illegible]t[illegible]ry D[illegible]i[illegible]on [illegible]f th[illegible] Am[illegible]c[illegible] Cya[illegible]m[illegible]d Comp[illegible]ny f[illegible]s[illegible]pplying the A[illegible]ros[illegible]l OT [illegible]d [illegible] these [illegible]t[illegible]di[illegible]

biotics accompanied by dietary supplements and vitamins Gradual improvement occurred upon this regime as manifested by a weight gain of 28 pounds return to normal temperature and an increase in the red blood count to 4 02 million.

The diarrhea and crampy abdominal distress continued however the patient passing an average of 4 to 5 watery evacuations daily without gross blood Aerosol OT in enteric coated capsules was administered orally in doses of 1 0 gm three times daily This medication continued daily for 66 days (FIGURE 2)

The patient continued to gain weight but the diarrhea remained unchanged and the stools were persistently guaiac positive without gross blood He continued to pass five watery stools daily and complained of abdominal distress intermittently while on Aerosol OT therapy Temperature blood count and sedimentation rate remained constant during and after the period of detergent administration

Proctoscopic examination, after 66 days of Aerosol OT therapy revealed marked pseudopolyposis pronounced granularity, friability and free bleeding accompanied by gushing of blood on cotton swabbing and numerous bleeding ulcerations Watery stools became more frequent and contained occult blood (guaiac 2+) After the detergent was discontinued the diarrhea and rectal bleeding persisted unaltered



F cuas 3 Eff t f os l OT po f cal ly zym

The following case report illustrates the lack of clinical response to 66 days of detergent therapy.

I. A., a 28 year old former Army Air Force major, first noted bloody diarrhea four years prior to admission to the hospital. He complained of cramping abdominal pain and severe bloody diarrhea six to twelve times daily, occurring intermittently over the four year period, and a weight loss of 30 pounds and severe anemia. Barium enema revealed marked polypoid changes with serration throughout the colon. Proctoscopic examination revealed an edematous friable, freely bleeding mucosa having small punctate ulcerations.

Although the patient had experienced several remissions during the four years prior to this admission, another exacerbation of his disease occurred six months prior to hospitalization. This episode was characterized by severe watery, bloody diarrhea six to eight times daily, a 50 pound weight loss, generalized crampy abdominal pain, fever to 102° F. daily, anorexia, nausea, and vomiting. One month later, following admission to the hospital, proctoscopy revealed a friable, freely bleeding, granular mucosa having numerous punctate hemorrhages. The red blood count was 2.4 million, total protein 4.7 gm. per cent, serum albumin 1.0 gm. per cent, globulin 3.7 gm. per cent, and sedimentation rate 25 mm.

Treatment consisted of a bland diet, multiple blood transfusions, and anti-

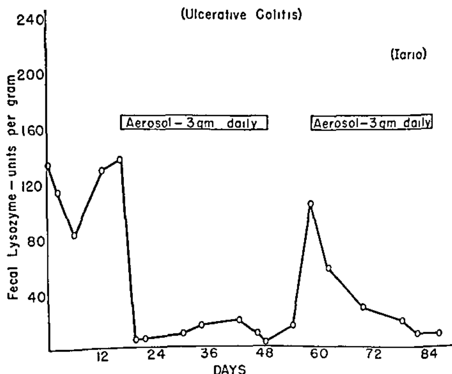


FIGURE 2. Effect of Aerosol OT upon fecal lysozyme.

DAYS	5	10	15	20	25	3	6	9	12	15	18	21	24	27	30	33	10	20	30	40	50
	Control Period					Hormone Therapy											Recovery Period				
STOOL LYSOZYME Units/gm																					
No of STOOLS	17	16	16	3	3	9	5	5	6	3	3	2	2	3	2		3		2		2
STOOL GUAIAC		3	3	3	2	2	3	2	0	0	0	0	0	0	0		0		0		
BODY WEIGHT Kilos																					
SED RATE		3									3		0								
HCT					3		33		30		3				3						
KETO STEROID			54								270			93							
MUCOSAL APPEARANCE																					
GRANULARITY					++++					++++				++							
FRIABILITY					++++					+++											
BLEEDING					++++					+++							0				
PSEUDOPOLYP					++					++				0			0				

Figure 4 Effect of hormone therapy upon ulcerative colitis

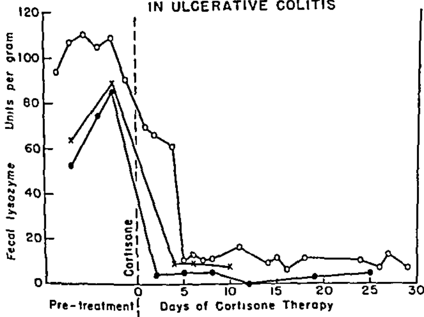


Figure 5

TABLE 3

EFFECT OF AEROSOL OT UPON THE FECAL LYSOZYME TITER OF PATIENTS WITH CHRONIC ULCERATIVE COLITIS

Patient	Control Period		Detergent Treatment (Aerosol OT)	
	Days prior to treatment with detergent	Lysozyme titer units/gm stool	Days of treatment with detergent	Lysozyme titer units/gm stool
B F	4	51	2	6
	2	68	6	11
	1	45	12	12
B U	4	85	1	11
	3	79	3	7
	2	152	4	7
	1	144	6	10
			8	2
			10	2
			12	7
B L	22	72	2	15
	21	85	8	29
	20	78	15	34
	9	45	16	21
	3	77		
O D	8	56	2	12
	3	56	4	12
			12	8
L E	19	462	2	20
	18	364	3	18
	13	303	7	17
	12	481	10	0
	8	220	16	0
	1	171		
			Aerosol discontinued	
			6	12
			21	19
			23*	20
			28*	132
			43*	220

* Days after Aerosol was discontinued

A similar failure in clinical response to detergent therapy was observed in a 22 year old woman (L. E.) who was given Aerosol OT in doses of 3 gm. daily for a period of 16 days. Her fecal lysozyme prior to treatment ranged from 171 to 462 units per gram. The fecal lysozyme was inhibited promptly by the detergent within 24 to 48 hours and was maintained at a level of 0 to 20 units for 16 days. When the detergent was discontinued, the lysozyme remained suppressed for an additional 23 days and then gradually returned to pretreatment levels (TABLE 3, FIGURE 3). Although the total period of time during which the lysozyme was suppressed was 39 days, no significant clinical improvement was observed during or after this treatment. The proctoscopic picture re

tent of the stools occurs within 2 to 10 days of therapy coincident with the remission This response is observed uniformly in all patients who respond favorably to hormone therapy

The rapidity with which a fall may occur is noted in FIGURE 5 The fecal lysozyme titer decreased to essentially normal values within the first five days of therapy in three of the nine patients studied (I I C R and M A) A more gradual decline in enzyme titer coinciding with the clinical improvement, was observed in patients H F O D, H K and M E *In each of these patients* higher pretreatment lysozyme titers were present probably indicating a more severe disease process (TABLE 4) *The difference in the rate of the lysozyme* fall may reflect the severity and duration of the disease process

The coincident fall in fecal lysozyme with the clinical remission of the disease is illustrated by patient O D (FIGURE 4) This patient demonstrated a gradual but definite decrease *in the fecal lysozyme content* over a period of 17 days of hormone treatment to levels characteristic of the chronic inactive state At the same time he experienced a reduction in the number of stools a definite decrease in the fecal loss of blood as well as a change in the consistency of the stools from the liquid to the solid state The clinical improvement was impressive between the first and second week of hormone treatment as evidenced by a sense of well being an increase in appetite and body weight a fall in the sedimentation rate an increase in the hematocrit and disappearance of fever and abdominal distress Definite proctoscopic evidence of remission appeared after one month of hormone therapy

In most instances repeated exacerbations and remissions in the disease are paralleled closely by increases and decreases in the lysozyme titer from initial levels of 100 to 150 units before treatment to 10 to 15 units during the remission period With recrudescence of the disease the lysozyme titer returns to the previous high levels *characteristic of the acute phase*

This striking relationship between an increase in the lysozyme titer during the recurrence of the disease may *be seen in* FIGURE 6 *In this patient* (M A) the titers before hormone treatment varied from 112 to 220 units per gram and diminished to the inactive levels of 15 18 and 13 units as the disease subsided during hormone therapy With the recurrence of an acute episode of ulcerative colitis four months later after treatment had been discontinued the lysozyme titer was again elevated to 110 127 and 65 units returning to the previous inactive remission levels of 24 16 and 10 units as the disease returned to the chronic quiescent stage

Hormone therapy appears to produce levels of fecal lysozyme in four to ten days which are characteristic of the remission phase of the disease seen in patients who recover spontaneously over a much longer period of time (TABLE 1)

Discussion

The lack of clinical improvement following the prolonged and effective inhibition of fecal lysozyme by the detergent raises some doubt as to the significance of lysozyme in the pathogenesis of the disease and suggests that the fecal lysozyme titer reflects a nonspecific tissue response to injury and inflammation

TABLE 4
EFFECT OF ACTH UPON FECAL LYSOZYME IN ULCERATIVE COLITIS

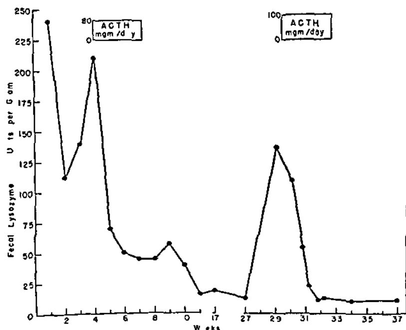
Patient	Control period (mean lysozyme units/gram)	ACTH therapy (mean lysozyme units/gram)	Recovery period (mean lysozyme units/gram)
F I	91	16	7
G R	71	4	2
H E	118	22	—
O D	234	43	5
H K	104	12	—
M E	207*	47	18
	177†	19	9
M A	79	8	—

* First hospital admission
† Second hospital admission

mained essentially unchanged, and the diarrhea, anorexia, blood loss, abdominal pain, and weight loss continued unaltered. The patient later on required ileostomy and colectomy.

The Effect of Adrenal Steroids upon the Fecal Lysozyme Titer

In contrast to the detergents, which effectively inhibit the fecal lysozyme titer without significantly altering the clinical course of the disease, the adrenal steroids often induce a definite remission accompanied by a consistent decrease in the fecal lysozyme titer (FIGURES 4 and 5). A prompt fall in the lysozyme con



F GU E 6 Eff t f ACTH pon fecal lysozym d m t t g the d f lt f cal lyso ym t t r a soci ted w th elapse a d emiss

average of 11 units per gram in a series of 29 patients in the inactive remission phase

(4) Repeated exacerbations and remissions in the disease were paralleled by increases and decreases in the fecal lysozyme titer

(5) The oral administration of a detergent (Aerosol OT) produced a prompt fall in fecal lysozyme to levels usually seen in the inactive phase of the disease

(6) The prolonged inhibition of fecal lysozyme by the oral administration of Aerosol OT did not alter the course of the disease or produce a remission in patients having ulcerative colitis

(7) Evidence was presented indicating that lysozyme does not play a significant role in the pathogenesis of ulcerative colitis It was emphasized, however that the inhibition of lysozyme in the feces by detergents does not necessarily reflect inactivation of the enzyme within the mucosal cells of the colon Moreover while lysozyme may not digest intraluminal mucus its mucolytic action on intracellular mucus is not known

(8) The administration of adrenocorticotrophic hormone or cortisone to patients having acute ulcerative colitis produced a significant and consistent decrease in the fecal lysozyme titer coinciding with the clinical remission in the disease process During hormone induced remissions the titers fell to levels usually observed in the inactive phase of the disease With exacerbations of the disease following discontinuation of the hormone therapy the lysozyme titer returned to pretreatment levels

(9) The fecal lysozyme titer appears to reflect the tissue s response to injury and inflammation It serves both as a measure of the activity of the disease process and the extent of the inflammatory reaction and parallels the clinical course of the disease

(10) The consistent and often dramatic fall in fecal lysozyme titers observed in patients responding to adrenocorticotrophic hormone or cortisone therapy follows a similar pattern to the inhibitory effects of these hormones upon other tissue reactions to injury

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and may thus serve as a measure of the activity of the disease process and the extent of the inflammatory reaction. *The inability of lysozyme to digest or dissolve colonic mucous in vitro*[9] is further evidence against its mucolytic action in ulcerative colitis and supports the thesis that lysozyme reflects the tissue's response to injury.

Further evidence in this respect is offered by the recent observations of Moeller *et al.* who produced increases in fecal lysozyme by subjecting the colon of an anesthetized dog to electrocautery.[10] Under these circumstances it was possible to reproduce levels of fecal lysozyme similar to those found in patients with ulcerative colitis. Hyperlysozymuria, moreover, has been noted in children having the nephrotic syndrome and various types of nephritis.[11] Despite the fact that these analyses were performed by a slightly different technique, it seems well established that hyperlysozymuria occurred in that group of patients having active renal disease and not in the group in the quiescent state. The finding of increased lysozyme in granulation tissue,[12] pus,[12] and the mucosa of acute rather than chronic gastric ulcers[13] further strengthens the hypothesis that lysozyme is the measure of a nonspecific tissue reaction to injury and, as such, is a good index of the degree and extent of tissue involvement.

It should be emphasized, however, that the inhibition of lysozyme in the feces by detergents does not necessarily reflect inactivation of the enzyme within the mucosal cells of the colon. Moreover, while lysozyme may not digest intraluminal mucus, its mucolytic action on intracellular mucus is not known. Evidence is accumulating in the literature showing the diverse ways in which adrenocorticotrophic hormone may alter the tissue's response to injury. Adrenocorticotrophic hormone, for example, is known to diminish the cellular reaction to injury by decreasing granulation tissue formation, and inhibiting fibroblastic proliferation. Its effect in reducing fibrinogen, complement and gamma globulin, and in inhibiting hyaluronidase (which acts upon a similar type of substrate as lysozyme) are all instances in which the tissue's reaction to injury is altered.

Gottschalk[14] and Hiatt[15] have shown that granulocytes, commonly present in large numbers in the stools of patients having ulcerative colitis, contain significant amounts of lysozyme. The decrease in lysozyme excretion following hormone therapy is probably caused by a diminution in the granulation tissue and a reduction in the number of granulocytes containing lysozyme in the stool. In addition, adrenocorticotrophic hormone may alter the ability of the tissue to react to injury, thus reducing the output of lysozyme at the cellular level, which further contributes to the fall in fecal lysozyme.

Summary and Conclusions

(1) The fecal lysozyme content of 30 normal subjects averaged 5 units per gram.

(2) In the acute phase of ulcerative colitis the lysozyme titer increased considerably to a mean of 100 units per gram. This was observed in 24 patients having active extensive ulcerative colitis.

(3) As the activity of the disease subsided, the fecal lysozyme titer fell to an

PANEL DISCUSSION

DOCTOR TRAVELL I should like to come back to Doctor Seed's paper and I should like to congratulate him on the type of study that was done It is exactly what we need in elucidating many questions in the pharmacology of cathartics for which we have no answers

I am a little bothered by the fact that he gave these magnesium compound one half hour after supper because the action of the salines usually depends on producing a peak concentration in the duodenum in a short space of time Also the pH is certainly different in the postprandial and in the digestive phases and according to clinical experience these materials would usually be given either at bed time in the evening or else the first thing in the morning on an empty stomach I should think we would get a good many complaints if we gave Epsom salts in the early hours of the evening We should certainly expect to get our patients up during the night

Were the amounts of water when administered with these saline cathartics kept constant in any way that being a factor in their action? Did Doctor Seed make any attempt to break down the results from his constipated people and his normals? May we also come back to Doctor Cattell's question as to whether there is any difference in the effect of these materials on the normal and the abnormal colon

DOCTOR SEED The questions are certainly very pertinent We have not tried to break down what happens in the very constipated patient *versus* the normal individual We should do that

The time at which the medication was given depended primarily on the convenience of the staff The dose that we gave of magnesium sulfate is one third the U S P dose In other word while the U S P dose is 15 grams we gave only five grams Our feeling was that even if you gave 15 grams of magnesium sulfate you would get a wide variation in time of response Even with a 15 gram dose some patients will not respond for 12 to 14 hours By and large most patients will respond in four to six hours so I think that the reduced dosage means that there will be a longer time for onset of action The higher the dose the shorter the onset time and that by and large really does not make too much difference The dose response curve of all these laxatives apparently is very much the same

DOCTOR TRAVELL How about the amount of water?

DOCTOR SEED We did not control the amount of water just water *ad libitum* That is another variable factor the background being randomized medication

DOCTOR TAINTER Throughout Doctor Travell's report she talked about the irritant laxatives and if I understood her correctly she included among the irritants the emodins cascara and senna primarily I do not know of any literature which would justify classifying these in the irritant group I myself have been calling them stimulant laxatives because senna particularly has been shown not to cause irritation If there were irritation it would be part of an inflammatory process I think in these which are rather mild in effect we

9 GLASS G B J B L PUGH W J GRACE & S WOLF 1950 Observations on the treatment of human gastric and colonic mucus with lysozyme J Clin Invest 29 12
10 MOELLER H C H C MARSHALL & J B KIRSNER 1951 Lysozyme production in response to burning of the gastrointestinal tract in dogs Proc Soc Exptl Biol Med 76 159
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12 PRUDDEN J F N LANE & K MEYER 1949 Lysozyme content of granulation tissue Proc Soc Exptl Biol Med 72 38
13 REIFENSTEIN I W S J GRAY H M SPIRO J C G YOUNG & E P CONNOLLY 1950 The relationship of lysozyme to other components of gastric secretion in peptic ulcer Gastroenterology 16 387
14 GOTTSCHALL G J PICKERING & D TABACHNIK Personal communication
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Discussion of the Paper

QUESTION What are the chemicals which reduce the lysozyme?

DOCTOR GRAY The aerosol has been continued for as long as 60 days in some patients and we were unable to demonstate any improvement Even though the lysozyme was kept down for over 60 days there was no clinical improvement that we could demonstrate

DOCTOR ALMY Is there any relationship between the amount of lysozyme and colonic mucus? In asking this question I might mention the interesting study by Kirsner and his associates on the production of increased lysozyme in the isolated colonic loop in the dog following stimulation with methacholine Is this due to stimulation of all secretions in the loop or to inflammation?

DOCTOR GRAY I would favor the last possibility that went along with an inflammation It is very difficult and particularly in the peritoneum to the stomach where you can change the secretions very readily We were never able to increase the lysozyme by any parasympathomimetic drug by insulin histamine or in any way that we could increase the secretion and I would guess that the same thing applies to the bowel I think it should be pointed out however that because of the inability of lysozyme to digest or dissolve colonic mucus *in vitro* while it militates against the mucolytic action in ulcerative colitis, we don t know what is going on inside the cell and whether lysozyme inside the cell will have an effect on the intracellular mucus It does not have an effect apparently on the intraluminal mucous

DOCTOR TAINTER If you mix aerosol with stool is the lysozyme neutralized thereby? Is the action entirely intraluminal which has no effect on what may be going on inside the cells themselves?

DOCTOR GRAY The *in vitro* studies were done by adding lysozyme to suspensions of stools containing the lysozyme The solution of aerosol was added to the solution of stool We don t know what is happening in the cell itself as far as the mucus secretion within the cell is concerned Nevertheless administering lysozyme over a period of 60 days and keeping the lysozyme at a very low titer did not seem to alter the course of the disease If we could inactivate the lysozyme inside the cell we don t know whether that would make a difference in the long term effects

we select about five patients out of 100 in the chronic disease group we find that you apparently need some bowel content modification and you can get it either by diet or by various other measures I think this would be desirable Whether you can get it by giving them a great many pills is another question We have tried teaspoonfuls of various medications but from the convenience point of view I don t see how you can deny the experience of thousands of years which shows that you have to give the patient whatever will produce an expeditious simple and satisfactory evacuation with a minimal effort on the part of the patient I think it is best to select a combination that is reasonable Some sort of combination is necessary

Doctor Ingegno *Do I understand correctly the best thing to do about laxatives when you have to use them is to use the mildest possible one that will have an effect?*

Doctor Travell That would be correct the object being not to produce a watery evacuation but to give the dose that will produce if possible a formed stool

Doctor Edward Burkhardt This discussion has not demonstrated what is the expectancy of a normal bowel movement in time or amount In my practice I have contended that from two a day to once a week is sufficient We seem quite preoccupied with the use of physic I wonder if we are not being sucked into a national neurosis I prefer to outline to the patients I see the normal expectancy First I ask them what they expect I ask them what would happen to them if they did not take a physic They go into details comprising abdominal pain headaches and lassitude So I treat all these things individually giving them aspirin for the headache phenobarbitol for the abdominal pain and dexedrine for the lassitude Then we start off with no physic and I ask them to call me at the end of the week if they have had no stool They accept that and if one can go on to the second week one generally has the problem licked It is a great deal like drug addiction To get off the peg is the main thing Some patients may have to be admitted to hospitals in order to restrain them from taking physic I am not talking about cases that have narrowed sigmoids due to diverticulitis or other obstructive features I think we as doctors have promoted the use of a great many physics Particularly, the enormous sales of Caroids and Bile Salts largely advertised through doctors is due to the fact that we have not taken time to make the patient understand what to expect of the normal stool I admit it has taken me at times as much as a year to get a person to understand that a stool once a week is normal

Chairman Cattell The point that has been made is certainly of great importance I wonder how many of the panel would agree

Doctor Gray I should go along with Doctor Burkhardt completely We very seldom use cathartics in the great majority of patients There are certain exceptions as in the case of a patient in bed for a long period of time and unable to get up Patients who are taking constipating medications for the treatment of ulcer for example may need a little help now and then but in the overwhelming majority of cases it can be handled by diet and psychological care

In a large institution such as Doctor Cass is contending with where you have

may have a stimulation of normal peristalsis with normal propulsive motions, but not irritation in the sense that the pathologist uses it

DOCTOR TRAVELL I think that is very true, Doctor Tainter The pharmacology of the emodin cathartics is very similar to phenolphthalein for which a stimulant action is probably the essential part of the mechanism It has not been possible to demonstrate local irritation from the magnesium compounds, and we don't know of any stimulant action which magnesium would have on the intestinal musculature We are inclined to believe, on the basis of the available evidence, that the effect is due to increased osmotic tension and retention of water in the intestinal tract We can demonstrate in animals that, in the presence of dehydration of a patient and shortage of available water supply the salines may be quite ineffective in producing the expected purgation We have made that experiment for years as a demonstration to the students

CHAIRMAN CATTELL In relation to the problem of dosage I should like to ask Dr Cass on just what basis he felt he could make useful comparisons of two dissimilar types of agents I think he did not obtain dosage response or did not attempt to relate side actions to the dosages that were used One apparent feature was that in a certain dose he could get an effective relaxing effect Do his conclusions go beyond that?

DOCTOR CASS I think that, with this type of study one can do no more than draw conclusions One aims his analysis at a precise objective Is this or that substance an adequate laxative? One can only determine the laxative effect on certain standards which one sets up and then one establishes an arbitrary dose One cannot say this is better or not better than the other One can only say this test indicates that a certain number of bowel movements will be forthcoming, because the bowel content is such and such and I do not think one should try to draw any conclusions beyond mathematical factors that are indicated by these results

DOCTOR ALFRED P INGEGNO We have heard a lot about laxatives Which is preferable to use?

DOCTOR TRAVELL Nobody wants to answer that Do you mean which is preferable of all the laxatives gums salines irritants or stimulants? Of course it would depend first of all on the condition for which it is being given Do you mean to imply in the application of this to the chronic constipation functional stasis which is best?

DOCTOR INGEGNO Yes

DOCTOR TRAVELL I thought the object was not to give a laxative Doctor Weintraub in a conference some time back said that he found very often it was impossible to change the patient s favorite cathartic pill so he just let him go on taking it and actually if one limits the use to the milder of these agents I should say that the choice is largely determined by the patient s preference and by a procedure of trial and error which the patient learns quite outside of anything that the doctor tells him

DOCTOR CASS May I say a word about that? From this technique that we use to determine the effect of laxation you are bound to get certain ideas of what is effective and after doing some of these studies it certainly seems that you get to that point In our extremely constipated group of people where

ful treatment The fact that he has not had a movement for two or three days is better controlled by having him go out and row on the river a couple of times a week get some fluid and exercise But the fact remains that in our group our test service gave placebos over a long period of time so we have no way of knowing until the end in what group the complaints were the greatest We did get a great many complaints in that placebo group which might be attributed to the insufficient number of stools rather than to any extraneous factors since it was not common in any other group I believe with Doctor Gray that in our particular group which was apparently definitely constipated both in consistency and frequency we may well need a laxative

DOCTOR ALMY This exposition of improved clinical methods for the evaluation of laxatives has been most impressive and I wonder if the same principles have ever been applied to the so-called antispasmodic drugs

DOCTOR INGEGNO They have been clinically but I don t think quite as well as they apparently have in the testing of constipation But I think Dr Almy that is actually what we should do and assess the value of these drugs clinically We are too ready to assume when we have obtained a certain effect that it is due to the antispasmodic If we use the random selection and the blind procedure that has been advocated for these laxatives I think our results would be much more valid

CHAIRMAN CATTELL What material would you use as criteria? What would you use in man for antispasmodic action as a criterion?

DOCTOR INGEGNO It would have to be the relief of symptoms relief of abdominal pain We are talking about man now not animals It would be the relief of symptoms the relief of bowel dysfunction That would be about all About the only other way that you could evaluate it in man would be on an experimental basis by kymographic studies for example but those of course are short term investigations For the long range the only way one could do it would be by an evaluation of the symptoms the response of the symptoms to the therapy I don t know of any other way

QUESTION It is thought the cholerae vibrio affects the colonic mucus This is thought to be the reason for the watery diarrhea The question is what is the substrate of lysozyme?

DOCTOR GRAY The substrate of lysozyme is a bacterium lysodeikticus

QUESTION In the bowel?

DOCTOR GRAY The substrate That is the whole point We tried to evaluate it at the close of the discussion The substrate for lysozyme in the human colon has never been identified or isolated If one takes mucus through a proctoscope of a patient with ulcerative colitis and add the lysozyme to it the mucus does not behave as the substrate for it Is that mucus denatured in the bowel? Is there a mucus upon which lysozyme acts intracellularly that we can not isolate or is there some other principle present that we don t know about?

thousands of patients, where you simply cannot, under any conditions, control the individual diet of each person, it becomes absolutely essential that some form of cathartic be used I can readily understand that or it may be necessary in the case of orthopedic patients who are restricted in bed for a long period of time Polio patients for example present problems, and another problem is in the case of the aged with atonic colon, where a little mild help may be needed We almost never go beyond milk of magnesia That is just about as strong a cathartic as is necessary We have had people come in and say they have had absolute intractable constipation yet these people may have a bowel movement two or three times a week without the use of cathartics The main thing is to get them off the cathartic habit and get them to have confidence in themselves Once you set up a vicious cycle there is just no end to it

DOCTOR TAINTER I think there is no question but that the less the amount of laxatives we use, the better the patient is provided you don t run into secondary effects which are equally undesirable Personally, I should question whether you are doing the patient much good by treating a relatively mild condition such as the use of cascara or milk of magnesia by getting him over on to benzedrine and phenobarbital It seems to me the withdrawal therapy with the antidotes for the laxative habit are therapeutically much more powerful potent and dangerous to the patient than the ones you treat

DOCTOR BURKHARDT Not for two weeks

DOCTOR TAINTER Yes you have a point there There is another side to this and that is that I question rather seriously whether a patient who has a bowel movement but once a week is normal We know that the colonic content is inspissated in the colon The longer the material stays in the colon the drier it is and the harder it is to evacuate I believe that on the basis of elementary physiology, a patient who retains the bowel content for a week until it is so hard and dry as to require a major struggle to evacuate it is very likely to suffer some disadvantage from the mechanical trauma that results Certainly the straining and tenesmus necessary at the stool is liable to produce hemorrhoids and other rectal complications The patient would be much better off if he had more frequent stools which were bulkier softer and easier to evacuate This is a mechanical argument Something maybe said about it in later papers when the proctologists tell us about the complications they see as the result of chronic constipation

DOCTOR TRAVELL In the beginning of my talk I tried to emphasize the difference in the use of cathartics in acute and chronic constipation which has been so well brought out already in the choice of a cathartic in the elderly patient confined to bed or in the orthopedic problem and other cases I should like to raise a question as to whether the gums are always the best agent to use With such substances do we not have to consider the possibility of excessive inspissation and drying out of the material with the consequent fecal impaction?

DOCTOR CASS We have a comparison in this type of problem In the Hygiene Department in Cambridge Mass we have a young group particularly from the law school to which we very rarely give a cathartic If a boy comes in with lassitude and complaints of bowel difficulty it is probably a question of examination tension and phenobarbital and dexedrine medication is a doubt

(Bargen s organism)[7] and the dysentery bacilli[8, 9] have all been suspected None of these has won widespread acceptance as a specific etiologic factor It has been proposed that chronic ulcerative colitis is a deficiency disease due to the absence of a factor present in preparations of hog intestinal mucosa[10, 11] It has been suggested that pancreatic enzymes under certain circumstances may initiate the disease by their effect upon the colonic mucosa[1] Allergy has been studied by numerous investigators[12, 13] Lium has produced ulcers in the explanted colons of dogs by prolonged spasm initiated by direct irritation parasympatheticommetic drugs and dysentery toxin[15] The ability of lysozyme to denude the intestinal tract of its protective mucous coating affords an attractive etiological hypothesis[16] but in explanted loops of intestine it has been impossible consistently to produce ulceration by the use of this substance[17] It is well known that nervous tension and altered emotional states affect the colon and often appear to bring on exacerbations[18] Functional colonic disturbances of psychogenic origin however almost never progress into chronic ulcerative colitis and most patients having chronic ulcerative colitis give no history of pre existing functional bowel disorders It is accordingly improbable that chronic ulcerative colitis is a purely psychogenic disease A critical evaluation of current etiologic hypotheses may be found in a recent review by Machella[8]

The initial pathological lesion in ulcerative colitis is either a perivascular aggregation of leucocytes or a crypt abscess at the base of one of the intestinal glands[19] Warren and Sommers recently reviewed pathologically 60 autopsied cases of ulcerative colitis and 120 specimens resected surgically Nineteen were characterized by vasculitis crypt abscess was the initial process in 71 and 90 cases were indeterminate There was no significant difference in the age incidence of the two types The vasculitis type affected women more frequently than men whereas the crypt abscess type affected both sexes with equal frequency The vasculitis type appeared to have a higher mortality than the crypt abscess variety most instances of vasculitis cases having been observed among autopsied cases The two distinct pathological types of ulcerative colitis could not be correlated with any of the classifications recognized clinically Both types of initial lesion appeared to lead to the same general gross appearance The lining of the diseased colon is deep red or purple from marked hyperemia or congestion and is wet and shining with blood and mucus Petechial hemorrhages are scattered over the surface the ulcers varying in number size shape extent and distribution Pus may be expressed from some of the smaller ulcers Larger ulcers may be confluent leaving only an island of mucosa on an otherwise denuded bowel Often there are longitudinal gutter like depressions extending the greater part of the length of the colon There may also be annular ulcerations so that there is a network of denuded submucosa with remaining boggy pseudopolypoid nodules With progression of the disease the wall of the colon is irregularly thickened Occasionally deep ulcers penetrate the muscularis so that only the subserosal connective tissue prevents frank perforation

When ulcerative colitis has healed either as the result of the natural course of the disease or from the effect of medication or after ileostomy the lumen is often narrowed and there may be an overgrowth of the surrounding mesenteric

THE NATURAL HISTORY OF ULCERATIVE COLITIS

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The natural history of a disease may be defined as its clinical and pathological course unmodified by effective therapy. In the case of chronic ulcerative colitis the etiology is unknown and no form of medical therapy has proved consistently effective. Therefore the course of the disease as witnessed by the clinician,[2] the radiologist and the pathologist presumably corresponds reasonably well with its unmodified natural history. Some cases of ulcerative colitis are altered by surgical treatment. In such cases the subsequent developments in the patient constitute the natural history of the disease as modified by surgery.

Ulcerative colitis may be defined as a nonspecific local or generalized systemic disease characterized at times of exacerbation by multiple ulcers in the colon usually giving rise to the passage of greater or lesser amounts of blood by rectum. In its milder form it is apparently localized in the lower rectum[3] which sometimes exudes small amounts of blood onto the surface of formed or constipated stools. On the other hand long standing ulcerative involvement of a major portion of the colon may be associated with profound systemic effects such as malnutrition anemia arthritis and skin manifestations. Moreover the disease is subject to acute fulminating exacerbations accompanied by high fever profound toxemia, and electrolyte disturbances of such magnitude as to constitute an immediate threat to life.[3,4] The patient having ulcerative colitis particularly in its well established chronic form is also likely to encounter any of a number of complications which include massive hemorrhage perforation stenosis fistula formation, polyposis and cancer. Accompanying the severer forms of ulcerative colitis there usually are profound emotional disturbances including depression and childish petulant negativistic behavior.[5] These disturbances are thought to be in part determined by the personality structure of the individual and in part by the toxicity of the disease itself.

Nonspecific ulcerative colitis is a disease of unknown etiology.[6] Diagnostically, it must be differentiated from acute and chronic enteritis bacillary dysentery amebiasis tuberculosis lymphogranuloma venereum carcinoma diverticulitis, and infestations of *Schistosoma japonicum* or *Balantidium coli*. Usually because of the characteristic appearance on sigmoidoscopic examination, the differential diagnosis causes little difficulty but in the small percentage of cases where the disease is limited to the right half of the colon the problem is not simple.

Many intensive efforts have been made to seek out the etiology of nonspecific ulcerative colitis. The earlier efforts were directed toward a specific bacterial cause: *Proteus vulgaris*, *Pseudomonas aeruginosa* *Aerobacter aerogenes* *Klebsiella pneumoniae*, *Proteus morgani* *Spherophorus necrophorus* beta hemolytic colon bacillus histoplasma, the fungus *Geotrichum* a gram positive diplococcus

(Bargen's organism)[7] and the dysentery bacilli[8, 9] have all been suspected. None of these has won widespread acceptance as a specific etiologic factor. It has been proposed that chronic ulcerative colitis is a deficiency disease due to the absence of a factor present in preparations of hog intestinal mucosa.[10, 11] It has been suggested that pancreatic enzymes under certain circumstances may initiate the disease by their effect upon the colonic mucosa.[1] Allergy has been studied by numerous investigators.[13, 14] Lium has produced ulcers in the explanted colons of dogs by prolonged spasm initiated by direct irritation, parasympatheticomimetic drugs and dysentery toxin.[15] The ability of lysozyme to denude the intestinal tract of its protective mucous coating affords an attractive etiological hypothesis,[16] but in explanted loops of intestine it has been impossible consistently to produce ulceration by the use of this substance.[17] It is well known that nervous tension and altered emotional states affect the colon and often appear to bring on exacerbations.[18] Functional colonic disturbances of psychogenic origin, however, almost never progress into chronic ulcerative colitis, and most patients having chronic ulcerative colitis give no history of pre-existing functional bowel disorders. It is accordingly improbable that chronic ulcerative colitis is a purely psychogenic disease. A critical evaluation of current etiologic hypotheses may be found in a recent review by Machella.[6]

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When ulcerative colitis has healed, either as the result of the natural course of the disease, or from the effect of medication, or after ileostomy, the lumen is often narrowed and there may be an overgrowth of the surrounding mesenteric

fat The major portion of the mucosa may be smooth but show patches of varying size with punctate or longitudinal pitted scars, and occasional or frequent pseudopolypoid tags

In cases originating as vasculitis the pitted scars are said to be deeper so that there are areas in the bowel wall akin to healed through and through infarcts There is often a considerable degree of fibrosis with foreshortening in the length of the colon and induration on palpation

Ulcerative colitis has been differentiated clinically by Bargen [9] into three types (a) thrombo-ulcerative colitis (considered by him to be a disease of specific etiology caused by a gram positive diplococcus), (b) segmental ulcerative colitis and (c) atypical ulcerative colitis Most observers describe two types classical ascending or left sided ulcerative colitis and right sided colitis [1, 22] Left sided ulcerative colitis is better understood because it can be followed sigmoidoscopically throughout its varying phases Although it may be accompanied by superficial injection and ulceration in the terminal ileum [23] it is rarely if ever seen in conjunction with true regional ileitis Right sided colitis may cause considerable diagnostic difficulty owing to the normal sigmoidoscopic picture It may be seen in conjunction with regional enteritis as ileocolitis Its predominant involvement of the ascending colon readily leads to confusion with such entities as amebiasis and tuberculosis Bleeding is not invariably present and one must consider in the differential diagnosis sources of small bowel diarrhea such as chronic pancreatitis and ideopathic steatorrhea

Ulcerative colitis whether predominantly right sided or left sided has variable clinical manifestations from a mild single occurrence to a series of severe fulminating episodes Ulcerative colitis of limited extent and severity is often described by proctologists as ulcerative proctitis It has been said that ulcerative colitis seldom spreads The portion of the colon involved in the initial attack may be recurrently diseased but in most cases new attacks fail to extend to previously undiseased portions of the colon Patients having ulcerative proctitis often appear in the office of the practitioner year after year with characteristic sigmoidoscopic changes limited to a portion of the rectum Their bowel movements may be formed or even costive and they show no evidence of systemic disease as reflected by the leucocyte count sedimentation rate body temperature hemoglobin determination or significant chemical changes Frequently the localized disease responds readily to instillations of bland substances such as nisulfazole The barium enema is ordinarily completely negative

More extensive ulcerative colitis may also be relatively benign if limited to a single attack or if recurrences are spaced at prolonged intervals Diarrhea is the rule and there is usually blood mucus and pus in the stools accompanied or not by moderate degrees of lower abdominal cramping or tenesmus The erthrocyte sedimentation rate is usually elevated but fever and leucocytosis are unusual unless the attack is relatively severe Early in an initial episode the barium enema is likely to be negative although after a period of time or during recurrences changes are likely to be noted On initial simoidoscopy the mucous membrane of the rectum and sigmoid is diffusely hyperemic and slightly edematous with or without spontaneous oozing of blood from multiple punc

tate ulcers too small to be visualized macroscopically Sometimes there are crescentic areas of bleeding from places touched by the open end of the sigmoidoscope during its introduction Characteristically, the mucosa bleeds from diffuse punctate sources when wiped with a cotton swab There may or may not be feculent mucopurulent material in the lumen of the bowel or patches of mucopus adherent to the bowel wall When the process subsides within a number of weeks the mucous membrane may return to an essentially normal orange pink color with a dry velvet sheen or there may be areas having a granular surface sometimes described as similar to cobblestones or to the skin of an orange

With repeated exacerbations or with a prolonged continuous course the X ray barium enema reveals definite evidence of abnormality The earliest finding by X ray is the appearance of snow flake or saw tooth serrations along the lateral aspects of the filled colon These serrations are supposedly caused by small flecks of barium sulphate in actual ulcer craters They are most frequently seen in the sigmoid and descending portions but the other portions of the colon may reveal their presence Later the thickening of the bowel wall leads to disappearance of the normal haustral markings and the appearance of a tubular bowel A further sequel is foreshortening of the colon accompanied by retraction of the splenic and hepatic flexures It is generally believed that that retraction and tubularization of the flexures occur late in the disease and represent an irreversible process Colons showing this degree of involvement by X ray have lost their ability to absorb fluid effectively so that diarrhea is an almost invariable *accompaniment In chronic continuous or recurrent ulcerative* colitis the barium enema frequently reveals scattered radiolucent areas interpreted as pseudopolyposis If the pseudopolyps are well established this picture is also irreversible but occasionally these shadows are caused by islands of mucosa in a bowel otherwise denuded to the level of the submucosa In such cases regeneration of the mucosa is sometimes indicated by disappearance of the radiolucent shadows on subsequent radiographic examination Ulcerative colitis in its chronic progressive or recurrent form may be accompanied by varying degrees of malnutrition weight loss protein depletion anemia and *asthenia and by such complications as arthritis erythema nodosa stenosis* massive hemorrhage and perianal disease most of which if severe are indications for surgical intervention which ordinarily can be carried out under elective conditions Carcinoma of the colon occurs in approximately 3 per cent of cases and is invariably fatal[21, 5] Its possible prevention constitutes one of the major reasons for more widespread employment of surgical treatment

An acute fulminating attack of ulcerative colitis occasionally occurs at the outset but more frequently as an unpredicted exacerbation of preexisting disease In such an episode the patient may rapidly decline into a state of critical illness *exhibiting a high septic temperature profuse bloody diarrhea* severe cramps and tenesmus anemia protein depletion electrolyte imbalance toxicity and profound emotional disturbances Large amounts of nitrogen are lost through the red and white blood corpuscles and the mucosal detritus in the feces Great difficulty is encountered in maintaining adequate protein intake because almost all foods lead to increased tenesmus and diarrhea Moreover

the patients characteristically develop a listless apathetic depressed emotional state and behave in a negativistic petulant manner when foods are offered them With acute fulminating attacks there is often ulceration deep into the muscularis of the colon and perforation is constantly to be feared Gaseous distension of the transverse colon is to be viewed with great alarm as a precursor of perforation If perforation occurs the rent in the bowel cannot be sutured because the consistency of the colon is like wet blotting paper One is faced with subtotal colectomy or with some type of exteriorization procedure Massive hemorrhages also occur and require subtotal colectomy According to Warren and Sommers the commonest causes of death are peritonitis, sepsis toxemia, renal insufficiency pulmonary embolism hemorrhage and emaciation However the outcome of fulminating ulcerative colitis is generally not fatal The most critically ill patients have been known to recover In an entirely unpredictable manner the temperature curve returns toward normal, the mental status improves the stools become less frequent, and the appetite returns In a period of weeks the patient reaches a state of partial or complete recovery but continues to have the prospect of further exacerbations in the future

In many patients, the natural history of ulcerative colitis is modified by surgical procedures of one sort or another In the past, such technics as appendicostomy, cecostomy ileocolostomy and ascending or transverse colostomy were sometimes carried out, but as none of these procedures diverts the fecal stream from the entire colon they have largely been abandoned It has been found almost impossible at operation to be certain which portions of the colon are entirely free from disease A surgical incision through even a mildly diseased colon is likely to be followed by failure of a suture line or by rapid activation of any colitic process which may be left within the path of the fecal stream Ileocolostomy is the procedure of choice with right sided colitis especially when the latter is seen in association with regional ileitis and the sigmoidoscopic picture is entirely negative However in most cases of primarily right sided colitis and in all cases of left sided colitis it is customary to divert the fecal stream by ileostomy and then to resect the colon in two or more stages

In some clinics ileostomy alone is carried out as the routine initial procedure and in others it is employed only in very sick patients thought incapable of withstanding more extensive surgery Following ileostomy there is usually gradual improvement in the toxic and febrile manifestations of ulcerative colitis There is often considerable difficulty maintaining electrolyte balance for the first two or three weeks postoperatively Sodium loss occasionally leads to states of collapse similar to those seen in Addisonian crises Ileostomy alone cannot be counted upon to stop massive hemorrhage It seldom relieves skin manifestations or arthritis The active mucosal inflammation in the colon diminishes somewhat, but the disease is not entirely arrested It is not unusual to witness a gradual contraction foreshortening and stenosis of the remaining colon

Subtotal colectomy from the cecum to the sigmoid is frequently carried out in conjunction with initial ileostomy or it may be undertaken as a second stage procedure after the ileostomy has become established Following subtotal colectomy there is less electrolyte disturbance than after ileostomy alone There is generally dramatic improvement in the welfare of the toxic patient and the

major risk of exsanguinating hemorrhage is removed For these reasons sub total colectomy and ileostomy are frequently performed together even in desperately ill individuals However subtotal colectomy usually fails to eradicate skin manifestations and arthritis or to relieve tenesmus and a foul smelling rectal discharge Moreover the diseased sigmoid colon and rectum remain as likely sources of carcinoma

The final state of modern surgery for ulcerative colitis is abdominoperineal resection of the sigmoid colon and rectum This eliminates all the hazards of the disease Many observers have noted that following final removal of the colon the terminal ileum takes on some colonic function in partially drying and solidifying the feces Thus the case of the ileostomy is simplified

The major problem for patients who have had their colons removed is the case of the ileostomy Bags have been developed in recent years which remain in place for several days when cemented onto the abdominal wall About one patient in ten has either stenosis or prolapse of his ileostomy This unfortunate individual is likely to have an unending series of revisions without permanent success in overcoming these difficulties Even stitching the mesentery to the posterior peritoneum does not invariably preclude prolapse

It is gratifying to note that following colectomy most patients do well from a socio-economic and emotional viewpoint This is true even of those who during the fulminating toxic stage of the disease appear to be hopeless psychiatric cripples The limitations of the basic personality remain but the patients usually get by remarkably well

Most patients having ulcerative colitis can be handled medically If surgery is undertaken promptly when indicated the disease has a comparatively low mortality The most unfortunate phase of the disease is the economic destitution so often brought about by loss of earning power prolonged hospitalization and medical expenses

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THE MEDICAL MANAGEMENT OF CHRONIC IDIOPATHIC ULCERATIVE COLITIS

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The medical management of chronic ulcerative colitis in our clinic consists of (1) the correction of specific deficiencies (2) the improvement of and the maintenance of a satisfactory nutritional status (3) the discovery of and attempts to solve the emotional problems underlying the disease and (4) the use of measures to control specific symptoms and situations

(1) The Correction of Specific Deficiencies

Dehydration and electrolyte (including potassium) imbalance if present are corrected by the administration of fluid and electrolytes by either the oral or parenteral routes depending on the indications in the particular case

Anemia is treated by transfusions of whole blood Iron is administered by mouth if the patient can tolerate it

Many patients suffering from ulcerative colitis are deficient in vitamins and such deficiency may be manifested by objective stigmata When vitamin therapy is decided on the vitamins are administered in adequate amounts and by routes which will assure their utilization

(2) Improvement of Nutritional Status of Patient

Most cases of ulcerative colitis present a nutritional problem The average patient has lost his appetite and is underweight The basic nutritional aims are (1) to supply an adequate amount of protein for the healing of a large area of inflammation and (2) to provide rest for the irritated bowel

One usually attempts to accomplish these objectives by the administration of a high-caloric high protein high carbohydrate low residue diet which is palatable adequate in vitamins and minerals and free of allergenic or irritating foods

It is sometimes not possible to achieve the objectives if one relies on ordinary foodstuffs The patient does not ingest an adequate amount of calories and continues to lose weight When faced with such a situation the problem may be solved by the administration of a solution of a mixture of a protein digest (50 per cent) and a carbohydrate (50 per cent) such as dextri maltose [1] Such alimentation meets all of the requirements of the basic nutritional aims except for inadequacy in iron and vitamins (including vitamin K) which must be supplemented

A measured amount of the mixture calculated on the basis of 20 calories per pound of preillness weight is dissolved in enough boiling water to form a 15 to 25 per cent solution and is stored in surgically clean milk bottles in a refrigerator Two hundred to 400 cc of the solution are administered every two hours from 6 A M to 10 P M

If the diarrhea persists or increases in severity a medical ileostomy [2] can

be performed by intubating the terminal ileum with a nasally passed Miller Abbott tube and preventing small intestinal content from entering the diseased colon by application of constant suction The solution of protein hydrolysate and dextri maltose is administered by mouth The use of medical ileostomy for a period of 10 to 14 days usually affords sufficient rest to the irritated bowel and permits subsequent administration of the nutrient solution without excessive diarrhea The solution is then administered until sigmoidoscopic evidence of healing is obtained (average case four to six weeks) after which a high caloric low residue full diet is gradually substituted The electrolyte and fluid balance is watched very closely during the period of withdrawal of ileal content in order to detect and correct disturbances promptly

In acute fulminating cases, fluids electrolytes and calories in the form of dextrose hydrolyzed protein and alcohol are administered by vein

(3) Discovery and Solution of Emotional Factors Underlying the Disease

An attempt is made to discover the emotional factors underlying the disease Our ability to induce a remission and to prevent relapses has been directly related to our ability to discover and successfully handle the emotional problems present The physician must be able to instill confidence in the patient, who is usually high strung and tense who is a hypersusceptible reactor to minor stress stimuli and who is as well hostile and resentful Frequently, an unsatisfactory parent patient relationship exists We always look for and frequently find impressive relationships between emotional stress onset of disease and the occurrence of relapses Most of the patients are handled by a member of our staff but in some instances the help of a psychiatrist familiar with the disease is sought Whoever attempts to handle the psychiatric aspects of the case is expected to do so in a tactful manner because unskillful dabbling may intensify the illness

Responsibility does not cease with the induction of a remission The patient is followed at frequent regular intervals and helped to ride out emotional storms in order to avoid relapses

(4) Other Measures

The various chemotherapeutic agents and antibiotics are not used in the treatment of ulcerative colitis unless suppurative complications threaten or exist We have found that such compounds do not appreciably alter the clinical course of the disease

We believe that the use of such agents for the purpose of suppressing or altering the bacterial flora of the colon is without much justification for the following reasons (1) Careful studies of the effects of the compounds on the bacterial flora have revealed that although it can be altered temporarily by sulfonamides after a while it resembles that of the untreated patient in type and quantity[3] (2) Studies have also revealed that a fecal flora resistant to antibiotics may develop more or less rapidly after continued administration of these substances (3) A lack of correlation has been found to exist between the changes in fecal flora brought about by the various antibacterial agents and

the clinical course of the disease (4) The use of some of the antibiotics particularly terramycin and aureomycin has been observed to cause diarrhea and ulcerative lesions in the colon[4] In fact, in some instances nausea vomiting diarrhea fever collapse and even shock have been attributed to the overgrowth of resistant strains of *Micrococcus pyogenes* (Staphylococci)[5] when the usual bacterial flora has been suppressed by aureomycin or terramycin

The results from corticotrophin and cortisone therapy have in many instances been dramatic The compounds have been used on the premise that ulcerative colitis is a stress disease In addition some patients manifest erythema nodosum and arthritis as well as a low level of adrenal activity as indicated by the finding of a decreased concentration of 17 ketosteroids in the urine ACTH is administered in amounts of 20 to 40 mgm intramuscularly twice daily for the desired period of time Cortisone, when used is administered by mouth or by injection The dosage schedule employed is as follows 100 mgm every eight hours during the first day 100 mgm every 12 hours on the second day then 50 mgm every 12 hours thereafter If a relapse occurs when the dosage is decreased the previous effective dosage is promptly resumed After about the 12th day the amount is gradually reduced to maintenance levels which in our experience varies from 37 5 to 75 mgm per day

When a patient responds to either ACTH or cortisone the response is usually prompt dramatic and accompanied by a sense of well being (often euphoria) a cessation of fever the return of appetite and a prompt disappearance of arthritis and erythema nodosum Diarrhea subsides promptly or gradually Roentgenological and sigmoidoscopic evidences of improvement lag behind subjective and objective clinical improvement as they not infrequently do after remissions induced by any other measures

Maintenance doses may be required unless emotional problems have been successfully solved otherwise relapses may occur When a relapse does occur on maintenance therapy a return to higher dosage schedules is indicated and will usually result in a subsidence of manifestations

We occasionally employ tincture of opium or powdered opium for the control of abdominal cramps and diarrhea and routinely administer one of the barbiturates Hot Sitz baths and the application of 2 per cent nupercaine ointment are used for the control of painful rectal conditions

The results of therapy with various medical regimens and the basis for their use have been recently reviewed[6]

The decision to operate on the intractable case is made when we believe that the emotional problems underlying the disease defy solution and salvage for economic or other reasons cannot be brought about by conservative measures When surgery is decided on the small intestine is carefully restudied roentgenologically for evidence of enteritis An ileostomy performed through a diseased terminal ileum may result in suppurative complications which will prolong convalescence

Summary

The medical management of chronic ulcerative colitis as employed in our clinic consists of the following

be performed by intubating the terminal ileum with a nasally passed Miller Abbott tube and preventing small intestinal content from entering the diseased colon by application of constant suction. The solution of protein hydrolysate and dextri maltose is administered by mouth. The use of "medical ileostomy" for a period of 10 to 14 days usually affords sufficient rest to the irritated bowel and permits subsequent administration of the nutrient solution without excessive diarrhea. The solution is then administered until sigmoidoscopic evidence of healing is obtained (average case four to six weeks) after which a high caloric, low residue, full diet is gradually substituted. The electrolyte and fluid balance is watched very closely during the period of withdrawal of ileal content in order to detect and correct disturbances promptly.

In acute fulminating cases fluids, electrolytes, and calories in the form of dextrose, hydrolyzed protein, and alcohol are administered by vein.

(3) *Discovery and Solution of Emotional Factors Underlying the Disease*

An attempt is made to discover the emotional factors underlying the disease. Our ability to induce a remission and to prevent relapses has been directly related to our ability to discover and successfully handle the emotional problems present. The physician must be able to instill confidence in the patient who is usually high strung and tense, who is a hypersusceptible reactor to minor stress stimuli, and who is, as well, hostile and resentful. Frequently, an unsatisfactory parent patient relationship exists. We always look for and frequently find impressive relationships between emotional stress, onset of disease, and the occurrence of relapses. Most of the patients are handled by a member of our staff, but in some instances the help of a psychiatrist familiar with the disease is sought. Whoever attempts to handle the psychiatric aspects of the case is expected to do so in a tactful manner because unskillful dabbling may intensify the illness.

Responsibility does not cease with the induction of a remission. The patient is followed at frequent regular intervals and helped to "ride out" emotional storms in order to avoid relapses.

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THE TREATMENT OF CHRONIC CONSTIPATION

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Chronic constipation is a peculiar disorder of both the bowel and the mind A patient suffering from this complaint may have somewhat unusual bowel habits but he is much more concerned with the significance of these habits Unavoidably his excessively bowel conscious attitude reflects the attitude of our culture in which the elimination of fecal waste has become inextricably interwoven with ideas of moral cleanliness and physical well being A few converts have been lost to be sure to the recent high pressure campaigns to make cancer the main concern of our lives but the colon enjoys a head start of about 5 000 years

Fifty years ago the emphasis on assiduous evacuation of the colon reached its tremendous peak We are apt to hold the food faddists and the cultists responsible but not only the Fletchers and the Kelloggs are to blame It was the age when Metchnikoff[1] could argue that only the evils arising from the large intestine prevented man from living 150 years when Sir Arbuthnot Lane performed colectomies (with a mortality of 24 per cent)[2] to restore happiness appetite and firmness of the breasts and was rewarded by having a book[4] dedicated to him as The Father of Stasis when balneotherapy hydrotherapy and massage competed to invigorate the lazy colon[5, 6] and when the medical literature could produce the following rhapsody[7] In the near Utopia stasis will be regarded as a sin more sinister than sedition surfeit more unseemly than schism fasts will become facts the function of the police will be the purveying of paraffin pilgrimages will be made not to Palestine but to Plombieres and Higginson shall be the high priest!

Except for a recent return to Metchnikoffian principles in the treatment of patients having severe liver disease[8] the vogue of autointoxication has been on the wane but ideas hang on tenaciously Many a physician still believes that the bowels have to be moved daily and some will discover constipation under any circumstances A case in point is that of the doctor who was visited by a young lady complaining of headaches

Your trouble is constipation said the doctor

But doctor I move my bowels regularly every day

That may be so was the authoritative reply but you re always 24 hours late

What does all this have to do with the treatment of constipation? The answer deserves bold emphasis For purposes of treatment constipation can not be thought of merely as a disorder of the colon and it should not be considered out of context with the often subconscious influences of the patient s cultural religious and personal background *Constipation may therefore be defined as a bowel habit which affects the patient psychically physically or both* This is the constipation we have to treat The number and consistency of the bowel movements *per se* very rarely warrant therapy The definition given

(1) The correction of specific deficiencies as promptly as possible These include electrolyte imbalance dehydration and anemia

(2) The use of measures to improve the nutrition of the patient by alimentation which provides as much rest for the colon as possible and gives a high calorie high protein diet as well as all of the essential vitamins

(3) The discovery and attempt to help the patient solve the emotional problems underlying the disease

(4) The use of hot Sitz baths and nupercaine ointment for the alleviation of painful rectal conditions

(5) The use of barbiturates to allay apprehensiveness and occasionally of opium preparations to lessen abdominal cramps and diarrhea

(6) The use of ACTH or cortisone is resorted to only in very ill patients, when other measures fail or cannot be carried out because of the urgency of the situation

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tion of the rectum is difficult when the feces are present in the form of scybala One or two of these hard pellets often remain behind to act as a continuing source of irritation to the rectum and eventually dull the sensibility of this organ to distention Seen in this light the constipation of the irritable colon is a disorder which affects the total evacuating mechanisms of the bowel, including not only the sigmoid but also the rectum In some patients voluntary anal opposition to involuntary attempts at colonic evacuation is probably the initiating mechanism which progressively disrupts the normal function of the rectum sigmoid and gastrocolic reflex Irrespective of the precise sequence of events in the pathogenesis of spastic constipation three reasonable aims of therapy would seem to be (1) relief of sigmoidal spasm (2) softening of the feces and (3) re-establishment of a normally integrated motility of the recto-sigmoid

The methods used in seeking these goals are, however not uniformly favorable from all viewpoints For this reason almost any regimen that is instituted for the treatment of spastic constipation is the result of compromise which in striving for good effects accepts some that are bad The use of antispasmodics of agents designed to soften the feces of dietary measures and of bowel training programs all exemplify the compromises that must be made

Antispasmodics Every antispasmodic clinically in use today whether tincture of belladonna or the latest anticholinergic of the quaternary ammonium type aims to inhibit the motor activity of the bowel From the viewpoint of inhibiting the nonpropulsive spasm of the sigmoid this action is theoretically beneficial Unfortunately these drugs if they work at all inhibit the propulsive as well as the nonpropulsive components of motility Consequently an antispasmodic may relieve sigmoidal spasm but may also lead to further stasis, further depression of the gastrocolic reflex [17] and further drying out of the feces in the sigmoid It may be argued that the antispasmodic effect compensates for any untoward action incurred as far as motility is concerned but it has not yet been settled whether decrease of sigmoidal spasm or promotion of normal propulsive evacuating mechanisms is more desirable in treating the constipation that goes with an irritable colon

From the practical viewpoint of clinical experience the use of antispasmodics is rather disappointing in the treatment of constipation Although undoubtedly effective in inhibiting the normal gastrointestinal motility of man or hypermotility induced by pharmacologic agents antispasmodics apparently are much less effective in treating the disorders of motor function occurring spontaneously or those induced experimentally by emotional stress [1] Some of the more potent agents while they may inhibit the motor functions of the colon also produce such marked side reactions that their total effect is detrimental rather than beneficial to a patient who suffers from a labile gastrointestinal tract Perhaps the best evidence for the limited clinical usefulness of the so-called antispasmodics is the continuing search for new agents and the frequent use of barbiturates with antispasmodics

Since the development of stronger and stronger anticholinergics appears to be reaching a point of diminishing returns at least as far as the treatment of spastic constipation is concerned different pharmacologic approaches deserve

takes a realistic view of the treatment problem and is not made to face the impossible task of defining a norm for healthy bowel habits

From the viewpoint of practical management, patients having constipation may be divided into three groups, but the division cannot be too sharply drawn since the distinguishing features of each group are found although to a lesser degree in the other groups as well Not included are such traditional classifications as atonic constipation, "rectal dyschezia' etc, since it is my belief that these mechanisms are rarely the cause of chronic constipation

Group 1 Imaginary Constipation

In the first group constipation is a matter of conviction rather than of fact Bowel movements are produced without any undue effort, abdominal and rectal distress are not experienced and the patient appears healthy as measured by ordinary objective standards Yet he complains of constipation for one of two reasons either the appearance and number of bowel movements does not measure up to the patient s expectations, or he blames such neuresthenic symptoms as headache insomnia and lack of energy on 'improper elimination Because of his anxious fixation on his bowel movements this patient often uses laxatives or enemas in spite of normal or potentially normal habits

The plan of treatment is simple The patient must be convinced that his bowel movements are normal or that they could be normal if he would only desist from abusing his bowel Successful execution of treatment is, however much less simple for the patients are often deeply disturbed and utterly convinced that their fecal waste lies at the root of all their troubles Success depends on how much reassurance and support of a general nature the doctor can give to the patient In some instances the patient s attitude and practices towards his bowel function can be corrected only to have the patient fix his anxiety upon some other innocent organ system Under such circumstances the general practitioner or the internist may have to turn to more specialized psychotherapy

Group 2 Spastic Constipation

The second group of patients does have physical complaints directly related to constipation The bowel movements are usually hard and scybalous and are expelled only with considerable effort Aching distress commonly located in the area of the sigmoid or cecum is a recurrent complaint and is frequently associated with a sense of incomplete evacuation after a bowel movement These symptoms indicate that patients in this group suffer from the disorder commonly known as irritable colon or spastic constipation Of all the types of constipation this one appears to be by far the most common

Clinical experience as well as investigations of the type described elsewhere in this symposium indicates that in spastic constipation the sigmoid manifests an excessive amount or degree of nonpropulsive motility commonly referred to as spasm thereby retarding the normal progress of the feces Probably as a result of the retardation the stools are dehydrated excessively and enter the rectum not as a sizable bolus but in small driblets which do not initiate the usual evacuating mechanisms of the rectum[9, 10, 11] In addition total evacua

before dashing off to work must accustom themselves to more substantial breakfasts

A bowel training regimen has one very serious drawback Patients who are already excessively conscious of their bowel are encouraged to be more so Short of pure psychotherapy, however this criticism is applicable to nearly all methods employed to combat constipation Stringent dietary regulations for example also keep the patient vividly aware of his colon for every time that he sits down to a meal he unavoidably thinks I must not eat this or that because it will hurt my colon Except in a few instances the beneficial effects of bowel training greatly outweigh the disadvantage particularly since the eventual purpose is the establishment of routine bowel habits independent of concentrated voluntary effort

Agents to soften the feces The establishment of satisfactory bowel habits by means of bowel training is greatly facilitated if the patient is given initially an agent that softens the feces This lessens the discouraging straining which takes place when the stools are scybalous and by facilitating rectal evacuation gives the patient the psychological lift often necessary if he is to persist conscientiously in a bowel training regimen for more than a few weeks Both the patient and the physician however must be fully aware that the ultimate aim is bowel movement without any artificial help whatsoever Consequently after the patient has achieved some success in his bowel training regimen the dose of the laxative is slowly reduced until it is eliminated altogether Reduction of the dose must be gradual, abrupt cessation may disrupt a regimen seriously

Two types of agents are available to soften the feces hydrophilic colloids and liquid petrolatum Both of these increase the water content of the stools both are relatively harmless and both can be easily administered in a gradually decreasing dosage The purpose and action of these agents should be explained to the patient and he should be warned in particular that he cannot suddenly effect a bowel movement by taking a large amount of one or another of these preparations

Whether liquid petrolatum or a hydrophilic colloid is preferable is a matter of some debate Although liquid petrolatum has been violently denounced [16, 17] my personal preference still lies with this agent The comparison of the two types of stool softening agents given in TABLE I is based purely on clinical impression and therefore should carry little weight Nevertheless two difficulties pertaining to the hydrophilic colloid are encountered often enough in practice to render their use less than ideal A number of patients experience a sensation of epigastric fulness and heaviness after taking the hydrophilic colloids a feature of hydrophilic colloid therapy which is sufficiently marked so that these agents have been introduced into the therapy of obesity Whether a mucilaginous mass may under some conditions form in the stomach to delay gastric evacuation is a point certainly deserving investigation The second disadvantage of the hydrophilic colloids is that frequently they are quite ineffective The patient who dries out his feces excessively also dries out hydrophilic colloids and on taking them frequently passes a gummy tenacious mass which in itself is not easily expelled from the rectum Studies are neces-

intensive trial C W Code[13] and the late W O Abbott[14] have emphasized the need for agents that lead to an integrated propulsive motility rather than to paralytic ileus The potential usefulness of such a therapeutic approach is indicated by the work of Adler *et al* [15] who induced effective propulsive motility in the human colon with several pharmacologic agents Particularly satisfactory was an apparently synergistic combination of ergotamine and prostigmine which stimulated colonic propulsion without causing any distress or side effects It is rational that spastic constipation should be treated with agents of this type in the morning Anticholinergics could then be reserved for use later in the day to alleviate distress and to permit more ready filling of the sigmoid from above

Bowel training If habitual disregard of, or actual opposition to the autonomic evacuating mechanisms of the colon eventually can derange these mechanisms the converse is possible, *i e* regular and repeated voluntary attempts at bowel movement might promote the re establishment of normal automatic function Upon a rationale of this type, the use of bowel training regimens in treating constipation is predicated

With diligence and perseverance nearly every healthy person under the age of 50 can make bowel habit a standard item of his daily routine To achieve this goal the patient must make an unhurried deliberate and consistent effort to move his bowels at the same time daily whether or not he has a desire to do so Obviously weeks and months of strict adherence to routine must be practiced before involuntary mechanisms can be expected to come to the aid of voluntary effort During this time the patient may temporarily feel more uncomfortable If he is forewarned that a certain amount of distress is to be expected while he is trying to break bad habits (*i e* laxative abuse irritating enemas) he is less apt to become discouraged with his necessarily slow progress

A program of bowel training is aided immeasurably by relating rectal evacuation to some standard antecedent stimulus This stimulus may be physical but is often predominantly psychic Thus patients establish gastrocolic or equivalent reflexes in which the stimulus for bowel movement consists of a cup of coffee a cigarette perusal of the morning paper or specific calisthenics The nature of the stimulus is however immaterial If the patient is convinced that two glasses of hot water with lemon juice will evoke a bowel movement two glasses of hot water with lemon juice is an excellent ritual for him to observe Confidence and conviction that a certain maneuver will work is the principal prerequisite for initiating a successful bowel movement

Although there is no harm in establishing a fetishlike stimulus for bowel movement it appears reasonable to strengthen more basic and less exotic stimuli For this reason the most satisfactory time to recommend an attempt at bowel evacuation is during the first hour after breakfast At this point intestinal contents have been moved downstream by the intestinal activity which is stimulated by waking getting up and moving about The ingestion of breakfast acts as a further stimulus to gastrointestinal motility and serves as a satisfactory means for initiating a gastrocolic reflex Implicit in this type of regimen of course is the need for most patients to arise somewhat earlier than usual and those whose habit it is to take nothing but a cup of coffee

TABLE 2

EFFECT OF DIETARY INTAKE ON WEIGHT OF FECES SOLID RESIDUE AND WATER CONTENT (AFTER RUBNER[9])

Food (per 24 hrs)		Feces (per 24 hrs)		
Type	Amount (grams)	Wet weight (grams)	Dry weight (grams)	% Solid matter
Mixed		131	34	26
Milk	3 075	174	41	23
Meat	1 434	64	13	20
White bread	1 237	109	29	27
Dark bread	1 360	815	115	14 2

by eating food containing relatively indigestible residues This is illustrated by the observations made 100 years ago by Rubner[19] and reproduced in TABLE 2 It is noteworthy that dietary bulk not only increases the solid fecal material but increases the water content to an even greater extent

Bulk is so often extolled by physicians as well as advertisers of patent medicines that it sometimes prescribed merely for the sake of obtaining more and bigger stools Since as has been emphasized the primary aim in treating constipation is the relief of mental or physical distress changing the character of the feces by administering bulk is a purposeless procedure unless the primary aim is thereby served In patients having spastic constipation the usefulness of bulk is particularly debatable since its beneficial effects are counterbalanced by its alleged irritant qualities Actually extreme ignorance prevails concerning the irritant effects imputed to high roughage foods Is bulk *per se* irritating to a spastic sigmoid? Does roughage in a physical sense scratch and traumatize the colon? Or are noxious products evolved by the action of bacteria on the substrate provided by the poorly digested residue? A few answers to these questions are available [0, 21] but by and large concepts as to the effect of various foods on colonic function are purely speculative Some of the meticulously rigid dietary regimens prescribed for the patient having spastic constipation illustrate the confusion that exists some vegetables are stringently forbidden whereas others of equal fiber content are recommended for daily consumption

Perhaps the most rational course for the physician is to advise a well rounded nutritionally adequate diet adjusted to the patient s tastes This plan avoids undesirable extremes of blandness or roughage and it does not indoctrinate the patient with dietary regulations of highly questionable validity

Water drinking Countless therapeutic regimens for constipation recommend the abundant drinking of water apparently in the belief that this routine produces softer feces Although it is undeniable that drinking one or two glasses of water on arising stimulates the gastrocolic reflex and may cause a bowel movement the idea that an extra daily intake of six to eight glasses leads to a proportional increase in the fecal water content lacks all objective evidence The monographs of Nothnagel and of Schmidt and Strausburger[3] state unequivocally that the amount of water consumed under ordinary conditions does not alter the consistency of the stools Hawk and his associates[4, 5]

TABLE 1
RELATIVE PREVALENCE OF UNDESIRABLE FEATURES OF LIQUID PETROLATUM AND HYDROPHILIC COLLOIDS

	Liquid petrolatum	Hydrophilic colloid
Ineffectiveness	+	++
Development of tolerance	++	++
Leakage	++	0
Gastric symptoms	0	++
Absorption of agent	+ (not clinically significant)	0
Colonic symptoms	+	++ (especially psyllium seed preparations)
Impaired food absorption	+ (not clinically significant)	?0 (no studies available)
Aggravate anal disorders	++	0

sary to determine to what extent hydrophilic colloids can oppose the reabsorption of water by the colon Finally it is my clinical impression that while hydrophilic colloids derived from psyllium seeds may be fairly irritable to the sigmoid this does not appear true of the synthetic preparations

Liquid petrolatum appears to be particularly undesirable in the presence of anal disorders which tend to be aggravated by this agent if for no other reason than that greater attempts at cleanliness must be carried out if the feces are oily As far as I am aware no disease has been described which can be blamed on the absorption of liquid petrolatum Consequently the dangers of its absorption appear to have been greatly overemphasized On the other hand except for taste the emulsified preparations of liquid petrolatum offer little advantage and if any absorption occurs these types are the most apt to pass through the intestinal barrier Particularly objectionable in this respect are *the mixtures of petrolatum and surface active agents now being marketed as* self emulsifying mineral oil The danger of vitamin A depletion also appears greatly overemphasized In adults taking the usual doses of liquid petrolatum (15 to 30 cc at bedtime) the carotene loss is of negligible proportions[18] The problem of leakage a definite problem that attends the use of mineral oil is not great if the patient has been given a proper schedule *i e*, small doses regularly ingested It must be admitted however that in some patients mineral oil will not mix with the stools but will leak' unpleasantly while the feces continue to be hard and pebbly

Many other maneuvers are used in helping patients to start a bowel training regimen Some physicians favor enemas of physiologic saline solution or rectal instillations of oil but bowel consciousness and anorectal irritation are no less promoted by procedures of this type and in general small doses of oil or hydrophilic colloids by mouth appear preferable to the rigmarole of frequently repeated clysters Irritant enemas containing agents such as soap are effective for acute cleansing of the bowel but like irritant laxatives they have no place in the treatment of chronic constipation

Dietary bulk The weight size and consistency of the stools can be altered

weapon in treating constipation A hasty comparison of the number of constipated with the number of psychiatrists indicates that wide open psychotherapy is hardly practical On the other hand every physician can and should incorporate into his reassurance and confidence building program certain simple psychotherapeutic measures Almy[7] suggests ventilation insight giving and provision of outlets for tension but it is my own feeling that such formalized and consciously identified measures are not necessary The sympathetic physician usually applies an indigenous and unnamed brand of psychotherapy provided that he recognizes the first essential that constipation is not merely a disorder of the colon.

Group 3 Rectal Insensibility

Although the etiology and mechanisms of the varieties of constipation in this group are both heterogenous and obscure certain features appear in common (1) the rectum is often filled with feces, (2) the feces are usually not scybalous (3) in spite of the fecal mass in the rectum the patient has no urge to move his bowels and (4) a vague abdominal sensation of bloating and heaviness rather than any real distress are the presenting complaints Patients in this category include a few that are psychotic a number of otherwise healthy young or middle aged adults and a great many enfeebled by age or invalidism

In those that are healthy and not too old attempts at restoring normal bowel function depend chiefly on the re-establishment of normal rectal sensibility For this purpose a bowel training program ranks as the single most important measure Stimulants of colonic motility such as prostigmine and ergotamine (which prove unexpectedly effective in some cases) and increased dietary bulk may be used as ancillary measures Since spasm is absent and the feces soft anticholinergics mineral oil and hydrophilic colloids are not indicated

Constipation in elderly patients especially those that have been dependent on laxatives for years and in patients debilitated by chronic illness is best treated by one of the wide variety of irritant laxatives available It does not appear worthwhile or even advisable from the viewpoint of their general health to put patients of this type through a campaign of bowel training and other therapeutic measures for constipation By and large laxation short of purgation is less exhausting than an enema or even a rectal instillation of oil If laxatives are used however the physician must recognize that he is not treating constipation in anything but a purely symptomatic manner Laxatives do not treat the *condition* of constipation in fact they accentuate perpetuate and fortify the sigmoidorectal disorders which underlie deranged bowel habits

Summary

For purposes of therapy chronic constipation is defined as a bowel habit which distresses the patient psychically physically or both Within broad limits patients complaining of chronic constipation tend to group themselve into three categories (1) those having imaginary constipation (2) those having

found that the daily weight of the stools was 105 gm when a subject was on a standard diet When 3000 cc of water were taken in addition, the average 24-hour stool weighed 74 gm!

From the purely theoretical point of view, it would be strange if a moderate increase in the usual quantities of water taken daily could escape the tremendous absorptive capacity of the human intestines Counting the water content of foods a normal man takes in about 2000 cc of water per day In addition the intestine reabsorbs digestive secretions amounting to some 4000 cc per day To state that an extra 1000 cc consumed per day escapes absorption and spills" into the rectosigmoid is to infer that the intestine has a maximal absorptive capacity for water a physiologic phenomenon that has not been demonstrated Actually, even huge excesses of water are easily absorbed, for they can be recovered almost quantitatively in the urine Only if enough salt is taken with the water to make the solution isotonic is it possible to counteract the highly efficient absorptive capacity of the human gut

Nevertheless so much authority recommends water drinking for softening the feces that it was decided to carry out the simple studies reported in TABLE 3 The results show what others have told us namely, that drinking eight glasses of water a day in addition to the regular diet does not alter the weight of the stools If doubt is entertained concerning these observations, it is suggested that these simple tests be repeated

In addition, it was found that the ingestion of an extra eight glasses of water a day is a difficult and unpleasant task if the usual fluid intake is scrupulously maintained We suspect therefore that patients instructed to drink extra amounts of water often reduce their usual intake of fluid

Psychotherapy Almy [6] has presented evidence that the abnormal sigmoid motility in patients having an irritable colon is a bodily change accompanying emotional conflict in response to environmental stress If as he maintains the heightened nonpropulsive motility of the sigmoid characteristic of spastic constipation *is principally the colon s way of participating in a hostile rigidly* determined behavior pattern then indeed psychotherapy should be our No 1

TABLE 3

AVERAGE DAILY WET WEIGHT OF FECES DURING THREE CONSECUTIVE 7 DAY PERIODS

(During periods I and III each subject took liquids and food according to his usual habits During period II eight glasses of water were taken daily in addition to the usual intake Under these conditions the wet weight of the stools is a satisfactory index of their water content)

Subject	Feces (average daily wet weight in gm)		
	Period I control	Period II water drinking	Period III control
1	54 1	63 2	81 6
2	10[illegible] 0	73 0	88 0
3	97 6	149 1	76 5
4	136 6	112 8	—
Average	99 25	97 68	82 03

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Summary

For purposes of therapy chronic constipation is defined as a bowel habit which distresses the patient psychically physically or both Within broad limits patients complaining of chronic constipation tend to group themselves into three categories (1) those having imaginary constipation (2) those having

irritable colons (spastic constipation), and (3) those experiencing diminished rectal sensibility All three categories require therapy at a mental level i e reassurance support, relief of tension and sometimes more formal attempts at psychotherapy Types two and three also require measures designed to promote normal sigmoidorectal function

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CHANGES IN THE COLONIC FUNCTION AND USE OF LAXATIVES IN THE AGED

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Constipation is probably the most common of all physical complaints in the aged. There is little doubt that the elderly individual tends to become bowel conscious and defecation often becomes the event of the day.

Etiology. The term constipation has many connotations. It may refer to a real or an imaginary complaint, or it may be a symptom arising from (1) an improper diet, (2) inadequate ingestion of fluids, (3) nervous fatigue and tension, (4) failure to respond to the call to stool, (5) lack of physical exercise resulting in atrophy of voluntary musculature, (6) a cathartic habit, (7) an atonic or hypomotile colon, or (8) real pathology.

Incidence. Mueller-Deham and Rabson[1] stated that one in every four old persons is habitually constipated, primarily because the diet lacks bulky foods that ordinarily stimulate peristalsis. Many habitually constipated patients give a history of the complaint as present since childhood. Humphrey[2] found in a study of 874 persons who had attained the age of 80, including 74 centenarians, that 31 per cent had constipation or took laxatives. However, Ivy[3] found that 31 per cent of 1082 college students also were constipated. Stroup[4] and Niles[5] have also concluded that there is no evidence that constipation is actually more common in the aged than in young persons.

Physiology. The activities of the colon are absorption, secretion and motility. Primarily water and salts are absorbed from the colon. There is no evidence that the absorptive and mucus-secreting capacity of the colon is decreased in old persons. Although there is considerable difference of opinion on the subject, many investigators emphasize the importance of distal colon stasis or malfunction as a cause of habitual constipation. It should be noted that the small intestine does not appear to play an important role in constipation. Sorter, Berg and Necheles[6] reported that constipation is one of the frequent complaints of their patients over 60, all of whom showed a lack of tone and contractile power of the sigmoid flexure and rectum. Constipation has also been attributed to redundancy of the colon secondary to atrophy of the muscles.[7] It was suggested by Freeman[8] that even though constipation presupposes slow motility, it is owing largely to rectal atony. Portis and King[9] are of the opinion that "left-sided" constipation is attributable to inhibition of the sacropelvic nerves subserving the rectum, sigmoid flexure, and descending colon. If constipation is of recent onset in the aged, it may indicate the presence of a neoplasm of the colon. Inadequate food intake caused by upper gastrointestinal disease such as pyloric obstruction may result in constipation. In our experience the use of aluminum hydroxide antacids and banthine[10] in the treatment of peptic ulcer may also be a causative factor in bowel dysfunction and may lead to severe obstipation. This must also be borne in mind in the use of such drugs as hexamethonium and apresoline (postganglionic blocking agents employed in the treatment of hypertension).

Psychological aspects The psychological aspects of colonic disorders have been studied A neuropsychiatrist[11] has reported that two of the paths that the aging organism takes in defending itself against the aging process are regression and conservatism Regression may reflect the relative importance placed on bowel movements in childhood Diarrhea has been considered to be a regressive phenomenon The second path of defense is conservatism and is manifested in old persons by a pattern of hoarding Conservatism is usually expressed in constipation which is said to be more common among men than among women Kantor,[12] however, stated that the most extreme constipation he had observed was among elderly depressed women In a recent study performed at the Geriatric Institute on a group of patients complaining of constipation we obtained good results with an accepted laxative but the results were equally good when the same group was given placebos

It is believed that fecal impactions occur not uncommonly in the aged Although the rectum remains over distended with feces a passage may be opened through the center of a fecal impaction and occasional watery movements may be evacuated Niles[5] regarded the development of the 'pecten band which limits distention of the anal canal as a pathological development of advancing years Colonic impactions (scybala) are seen occasionally in old bedridden individuals having intermittent or intractable diarrhea as the major symptom An irregular sausage shaped mass may be demonstrated in the transverse or descending colon by palpation Such an impaction may even simulate carcinoma of the colon Since barium sulfate tends to form particularly firm impactions patients should receive an adequate dose of a cleansing laxative such as milk of magnesia following X ray studies

Diverticulosis Although it has been frequently stated that the colon atrophies and its musculature becomes thin and atonic with age real evidence supporting this view is lacking The increased incidence of diverticulosis of the colon accompanying advancing age has been used as an argument favoring the thinning of the colonic musculature Diverticulosis of the colon is rare below the age of 35 Others believe that pressure in the colon causes diverticulosis only in those persons who have inherited or have constitutionally a colon having areas anatomically deficient in elastic and muscular tissue Diverticula of the colon are demonstrated so frequently by roentgenologists that one is led to believe that they are present in the majority of individuals over 60 years of age[13] They may be found scattered at various points along the ascending transverse, and descending colon but it is estimated that about 60 per cent are concentrated in the sigmoid area Ivy[3] stated that diverticula are about 33 per cent more frequent in women than in men while Valdez[14] said that diverticulosis is commoner among men

Portis and King[8] reported that in 96 elderly patients the colon was normal in 51 redundant in 11 and irritable and spastic in 34 Forty six patients (34 6 per cent) had diverticula Only 14 of the 46 patients with diverticula were constipated 25 had regular bowel movements 5 had diarrhea and 2 had alternating diarrhea and constipation

We wish to stress that diverticulosis *per se* is not a disease and that it is not

wise to prescribe a blind diet or lubricating oils just on this finding No treatment at all is best, if we are able to exercise restraint

Diseases of the colon Diverticulitis is a well recognized clinical entity It is a true inflammatory process accompanied by localized tenderness fever and leucocytosis It does not appear to be induced by roughage in the diet nor by constipation but it may be intensified by catharsis Gross hemorrhage is not uncommon and some cases of it progress silently to abscess formation and peritonitis The inflammatory mass may cause intestinal obstruction or may even suggest cancer Such a case requires surgery Less severe cases may be kept under observation in the hope that they will respond to antibiotic therapy

The incidence of ulcerative colitis and mucous colitis is relatively rare in patients over 60 years of age

Statistically, we find that 85 to 90 per cent of malignant lesions of the colon are in individuals over 40 years of age and 60 per cent occur between the ages of 50 and 70 The adenomatous type of polypoid lesion of the colon is more common than is generally considered Approximately 70 per cent of all polypoid lesions can be seen with the sigmoidoscope Because of the changes of malignant degeneration polyps should always be removed [15]

In a review of 1000 cases of carcinoma of the colon Boyd *et al* [15] found that over 80 per cent of tumors of the large bowel irrespective of location had pain or discomfort referable to the right lower quadrant It is interesting to note that 17 per cent of these patients with carcinoma of the colon had been subjected to appendectomy

The usefulness of the cytological method of diagnosis in detecting polyps and cancer of the rectum and of the lower intestinal tract following rectal and colonic washings has recently been demonstrated by Bader and Papanicolaou [16] There were 19 cases in their series of 200 patients that proved to have cancer by biopsy or surgery and 18 of these had positive or suspicious smears These results seem to justify the conclusion that the cytological method is dependable as a laboratory diagnostic procedure and that it has particular usefulness in the diagnosis of lesions beyond the reach of the sigmoidoscope

Hemorrhoids fissures and strictures of the anus may painfully narrow the passageway and they are often associated with bowel dysfunction

Some of the more common causes of diarrhea in the aged are acute infectious enterocolitis amoebic infection idiopathic steatorrhea deficiency states with hypoproteinemia avitaminosis such as pellagra and sprue and chronic pancreatic disease Biliary disease especially with fistulae between the biliary and intestinal tract may be a cause of diarrhea Patients who have had their gall bladders removed may have several urgent bowel movements in the morning for months or years afterward A few patients suffering from achlorhydria have diarrhea characterized by several formed or loose stools usually in the morning Their symptoms can often be alleviated by small doses of hydrochloric acid

Fermentative diarrhea is not uncommon in old people Excessive amounts of starch in the diet particularly bread and potato set up a cycle of alternating

diarrhea and constipation The starch is fermented by yeasts in the bowel Abdominal distention and flatus may result from the accumulated gas The copious, mushy stools are acid to litmus paper and contain material that stains blue with iodine Fermentation diarrhea can be treated effectively by substituting rice for the bread and potatoes for rice does not appear to ferment Vitamin B also seems to hasten the improvement but the quickest results follow cleansing of the bowel contents by castor oil

Medical Management The most difficult situations to treat are the colon disorders resulting from the prolonged use of laxatives Probably the most important part of therapy is to convince the patient that daily bowel movements and laxatives are not essential to one s general health Reassurance by the physician is an important psychotherapeutic measure in overcoming bowel consciousness

Instructions for treatment of constipation should include

(1) *Diet* The plan behind the diet for the relief of atonic constipation is to supply material which is not absorbed to any great extent by the small intestine but passes on to the colon and adds bulk The diet should therefore include adequate amounts of fruits vegetables and salads

(2) *Habit* Regular hours for meals and for visiting the toilet should be established

(3) *Fluids* The intake of adequate amounts of fluids *i e*, three liters daily is of the greatest importance As a practical measure elderly patients should be encouraged to drink adequate fluids during the day and less at night so that their sleeping hours will not be distrubed by nocturia

(4) *Cathartics* An attempt should be made to withhold all cathartics during the period of re education Only in the very feeble or bedridden cases should continuous reliance be placed on cathartics An occasional patient may require retention enemas of warm tap water to ease the passage of the dehydrated stool Inactivity poor nutrition and inadequate hydration are important underlying factors in their constipation Saline cathartics and excessive fluids however are contraindicated in elderly patients with congestive heart failure

(5) *Prunes* The laxative effect of prunes has long been established Recent investigations have shown that prunes and prune juice provide not only cellulose but the stimulant factor disphenyl isatin[13]

Patients having unstable autonomic nervous systems may alternate between constipation and normal or increased bowel activity Constipation is a functional disorder wherein the colon or segments of it may be spastic and/or atonic It has been well established that segmental atonicity and spasticity may coexist and result in a derangement of the propulsive mechanism of the colon Atropine is contraindicated as an antispasmodic in elderly people for fear they may develop glaucoma Homatropine methyl bromide (novatropine or novatrine) 1/49 to 1/23 grain (1 3 to 2 5 mgm) four times a day may be substituted or small doses of phenobarbital or chloral hydrate may help to prevent overstimulation of the gastrointestinal tract in elderly individuals

Since hygienic measures are sometimes inadequate in the treatment of constipation supplementary action must be used Wechsler[15] incidentally reported

that in a series of twelve cases only three were found to show X ray evidence of prolonged emptying time owing to an atonic colon to substantiate their bowel complaints Good tone was observed in the remaining cases It must therefore be assumed that bowel complaints in the aged are to a large extent psychic in origin and any evaluation of laxatives suffers from the mental fixations common to this age group

Bowels of good tone when put under reasonable tension owing to bulky contents should function according to the accepted laws of smooth muscle activity Since it is difficult for many elderly individuals to include adequate amounts of fruits and vegetables to provide bulk the tendency in recent years has been to add a variety of hydrophilous colloids of the methylcellulose type to the diet [19] These inert colloids increase the volume of the stool and prevent inspissation and hardness The function of the bowel can be greatly improved by the addition of methylcellulose in such conditions as an irritable bowel associated with constipation or diarrhea intestinal stomas and the milder forms of infectious diarrhea It should be noted that the consumption of large amounts of fluids required with bulk laxatives is often difficult for a geriatric patient Furthermore a change of laxatives after years of service with another is not welcomed

Portis and King [9] were of the opinion that if the muscles could be efficiently stimulated pharmacologically evacuation of the bowel would be more regular Because the evacuation reflex is carried over the sacropelvic parasympathetic nerves they administered neostigmine to a large number of ambulatory patients This drug abolishes the cholinesterase influences on acetyl choline and allows the latter to act unimpeded on stimulating muscle contraction thus overcoming constipation It also stimulates the glandular structures in the mucous membrane The drug was administered in doses of 15 mgm three times a day with satisfactory results and without untoward reactions

Sorter[6] reported that a group of 17 patients having senile constipation were treated with daily oral doses of 30 to 80 mgm of urecholine Only four patients of this group obtained beneficial results Another group of 37 patients suffering from senile constipation were treated with a preparation of the purified water soluble extract of cascara sagrada (peristaltin) Satisfactory results were obtained in 79 per cent of the cases The use of this drug seems to be a contribution by the Indians of California who used the bark of the cascara tree for the treatment of constipation Susceptibility is not lost with prolonged use and the establishment of regular habits permits gradual reduction of the dose although complete withdrawal of the drug is not always possible

Constipation may also be overcome by stimulating production of bile the normal laxative of the digestive tract This stimulation is accomplished by inducing choleresis with dehydrocholic acid (decholin or ketochol) in 3 to 5 grain (20 to 30 gm) doses at mealtime Dehydrocholic acid is preferred to bile salts which serve as cholagogs

Drastic cathartics such as mercurous chloride (calomel) rhubarb sodium phosphate magnesium sulfate (epsom salts) and magnesium citrate should be avoided Such harsh cholagogues and cathartics may result in irritation of the mucous membrane or so called cathartic colitis [20] Often stimulant laxatives

lead to loose watery stools Constipating medication may be subsequently ordered resulting in intermittent diarrhea and constipation Diarrhea in the aged is fatiguing dehydrating and, most important, it is often followed by constipation accompanied by danger of fecal impaction and obstruction

A large number of the cases of so-called nervous indigestion characterized by motor disturbances are undoubtedly attributable to the cathartic habit In a survey of 3000 cases 22 per cent of the men and 33 per cent of the women took cathartics or enemas every day or several times each week

Epstein[21] observed that patients receiving digitalis for cardiac conditions are less prone to suffer from intestinal stasis It was common practice among veterinarians to administer large doses of digitalis per rectum to horses, in order to combat "wind colic," a common and often fatal malady among these animals Epstein has applied this method successfully in the treatment of constipation in adults However the exact mechanism by which digitalis establishes peristalsis is still problematic

In conclusion it can be stated that no single definition accurately describes all types of constipation, particularly in the aged A bowel fixation appears to be the underlying cause of their complaints of constipation since prolonged emptying times of the colon cannot be demonstrated in most patients In our experience although the milder laxatives and even placebos induce objective improvement most patients prefer to return to the irritant laxative to which they have been addicted Because of the psychological fixations in the elderly, the risk of evaluating drugs on subjective findings only should be given proper recognition by clinical investigators

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THE PROBLEM OF CONSTIPATION IN THE INSTITUTIONALIZED PATIENT

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If the cathartic consumption in institutions were to be examined, no one would question the fact that there is a problem of constipation in the institutionalized patient. Through the courtesy of Dr. Newton Bigelow * it is known that for the year of 1952 in 28 New York State mental hospitals an extraordinary amount of medication was prescribed to overcome presumably, "bowel stasis." Cascara sagrada, the most popular medication, amounted to 615,000 of the 739,000 cathartic tablets consumed. Of the 4,272 gallons of liquid preparations used, mineral oil accounted for over 1600 gallons. Apparently, mild cathartics are insufficient for this type of patient, for 17,500 pounds of magnesium sulfate were also consumed.

In institutions other than mental hospitals the consumption of cathartics may also be very high. In the Bird S. Coler Memorial Hospital and City Home, an institution for chronic disease and custodial care which has recently been opened, it has been noted, almost from its inception, that the cathartic problem would require considerable attention. For a brief three month period, the cathartic consumption for approximately 550 patients averaged 14,300 doses, which means that every patient received 26 doses of a cathartic during this period, or approximately one dose every three days.

Recognition of the problem is the first step towards adequate therapy. The fact that tremendous quantities of cathartic medications are in use in chronic disease institutions should cause us to reflect as to the possible reasons and etiological factors. The problem has many facets which cannot be lightly dismissed by just noting the quantity of cathartics that are consumed. First of all, *does the cathartic load represent constipation or does it reflect the prevalent* attitude by many functionaries associated with chronic nursing care that the daily bowel movement is a "must" and a required routine occurrence? In other words, does the patient actually require a cathartic because there is some delay in bowel function, or does the attending physician or nurse prescribe a cathartic routinely, although the patient experiences no discomfort from the delayed function which may be normal for that particular patient?

Patients in chronic disease hospitals for custodial care present another interesting facet for cathartic administration. These patients, regardless of the underlying disease, are frequently hospitalized for permanent care because of lack of relatives or inadequate home facilities. The patients often vegetate with few or no breaks in their daily routine living. They seldom fraternize with other patients and tend to withdraw within themselves. Day in and day out, their only contact with reality is their own physical disability and the relationship of this malady to the amount of individual care available to them by the nurses and attendant staff. Patients soon learn that additional attention

* Commissioner, Department of Mental Hygiene, State of New York.

is possible if they complain of lack of bowel movement Since the nurse may spend a few minutes more each day with the patient satisfaction of the complaint has gratified a social void Instituting group fraternization and occupational therapy has decreased this form of 'constipation in our patients

Unfortunately the afore-mentioned factors have been overlooked in evaluating the actual need for cathartic agents and the abuse of these factors has deflected our attention from the real problem of bowel dysfunction

An institutionalized patient who presents the problem of delayed bowel movements must be considered from several points of view It must be determined first whether the constipation was present before the patient developed the particular medical condition which led to his being institutionalized or whether it occurred as a result of the disea e state or secondarily to the institutionalization Next it must be determined whether the existing constipation is of temporal significance whether the fecal content because of its hard consistency is the major difficulty or whether both factors are playing a role in the patient s complaints A bowel movement of normal consistency but occurring every third or fourth day may not be actual constipation except in the sphere of psychological disturbances motivated by undue significance attached to the act of defecation Conversely a patient may be considered constipated in spite of daily bowel movements when the stools have become firm and dry with resultant increased effort required for bowel function Since such an effort may be detrimental to the patient s welfare as in the case of a cardiac this condition may be a serious form of constipation For institutionalized patients a change in consistency of the feces to hardness is of greater significance than temporal alteration *per se* The third problem is to determine the reason for the temporal alteration or change in stool consistency and to analyze the pathogenesis of its occurrence so that appropriate therapy is possible There is no greater error made in the care of institutionalized patients than to recommend routine standard measures to increase bowel function without regard to the multiplicity of factors that may be operating in a particular patient The use of laxatives by themselves may only accentuate the problem rather than correct it

The accompanying classification (TABLE 1) considers the various factors for constipation that may be a problem in the institutionalized patient From a practical point of view most patients adjust themselves to the psychological and environmental factors Bedridden patients accept the inevitable bedpan and soon manage without much difficulty It is not unusual for the patient to accept the lack of complete privacy with the rationalization that after all he is ill and that allowances must be made for hospital facilities This type of constipation does not require any therapy except that of willful neglect Lack of recognition of the eventual self correction and zealous use of laxatives during this phase of the hospitalization may perpetuate the constipation into the chronic sphere

Medications of value for the treatment of the underlying medical or surgical conditions may result in constipation for a multitude of reasons Opiates particularly morphine and codeine and their derivatives are notorious in this regard From a pharmacological point of view this constipating effect may

THE PROBLEM OF CONSTIPATION IN THE INSTITUTIONALIZED PATIENT

By Robert C Batterman
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If the cathartic consumption in institutions were to be examined no one would question the fact that there is a problem of constipation in the institutionalized patient Through the courtesy of Dr Newton Bigelow,* it is known that, for the year of 1952 in 28 New York State mental hospitals, an extraordinary amount of medication was prescribed to overcome presumably 'bowel stasis' Cascara sagrada the most popular medication, amounted to 615 000 of the 739 000 cathartic tablets consumed Of the 4,272 gallons of liquid preparations used mineral oil accounted for over 1600 gallons Apparently mild cathartics are insufficient for this type of patient, for 17 500 pounds of magnesium sulfate were also consumed

In institutions other than mental hospitals the consumption of cathartics may also be very high In the Bird S Coler Memorial Hospital and City Home an institution for chronic disease and custodial care which has recently been opened it has been noted almost from its inception, that the cathartic problem would require considerable attention For a brief three month period the cathartic consumption for approximately 550 patients averaged 14,300 doses which means that every patient received 26 doses of a cathartic during this period or approximately one dose every three days

Recognition of the problem is the first step towards adequate therapy The fact that tremendous quantities of cathartic medications are in use in chronic disease institutions should cause us to reflect as to the possible reasons and etiological factors The problem has many facets which cannot be lightly dismissed by just noting the quantity of cathartics that are consumed First of all does *the cathartic load represent constipation or does it reflect the prevalent* attitude by many functionaries associated with chronic nursing care that the daily bowel movement is a must and a required routine occurrence? In other words does the patient actually require a cathartic because there is some delay in bowel function or does the attending physician or nurse prescribe a cathartic routinely although the patient experiences no discomfort from the delayed function which may be normal for that particular patient?

Patients in chronic disease hospitals for custodial care present another interesting facet for cathartic administration These patients regardless of the underlying disease are frequently hospitalized for permanent care because of lack of relatives or inadequate home facilities The patients often vegetate with few or no breaks in their daily routine living They seldom fraternize with other patients and tend to withdraw within themselves Day in and day out their only contact with reality is their own physical disability and the relationship of this malady to the amount of individual care available to them by the nurses and attendant staff Patients soon learn that additional attention

* Commissioner Department of Mental Hygiene State of New York

with these gastrointestinal medications should be kept in mind and frequent enemas used to forestall fecal impaction

Dietary factors play a large role in the production of constipation in the institutionalized patient As a rule diets are soft and lacking in roughage From a practical point of view, such a diet meets the requirements in terms of therapeutic necessity for the majority of patients When meals for hundreds of patients are prepared in a central kitchen it is impossible except under very unusual circumstances to arrange a special diet for any particular patient Patients who digest and utilize their food almost to completeness will have very little residue for proper gastrointestinal motility and subsequent stimulation of the defecation act Since dietary correction may not be possible it must be remembered that a temporal alteration because of lack of sufficient feces is not too significant and not by itself an indication for cathartic agents

Bed rest in itself may be an extremely important etiological factor for the development of constipation We accept without question the mechanical factors associated with bed rest, but what is not readily appreciated is the profound metabolic disturbance that may occur secondarily to chronic inactivity associated with bed rest In addition to progressive loss of muscular tone skeletal as well as gastrointestinal the body in an effort to conserve nitrogenous products to forestall or counteract a negative nitrogen balance will produce diminished gastrointestinal secretions with a decreased enzyme content This development in turn because of digestive abnormalities results in disturbances of gastrointestinal motility The high incidence of achlorhydria and gastrointestinal complaints in bedridden debilitated patients is in my opinion related to this disturbance in nitrogen metabolism Replacement of gastrointestinal enzymes has been successful in controlling the many functional gastrointestinal complaints of these patients and correcting this form of constipation

The problems of gastrointestinal motility disturbances have already been considered in part They may be primary reasons for constipation but more often they are the possible explanation for other factors Of greatest importance are diseases of the nervous system Disturbances in autonomic nervous system balance accompanied by abnormal reflex activity of any portion of the gastrointestinal tract may result in atony or localized spasm Many authorities consider this factor as the commonest form of chronic constipation If however an imbalance of the autonomic nervous system is a contributory factor use of those drugs acting on this system would be more rational than use of cathartic agents *per se* Combinations of laxatives which stimulate gastrointestinal motility and antispasmodics to decrease or abolish the irregular areas of spasm may be of value in such patients

Disturbances in the act of defecation are the most important reasons for chronic constipation Emphasis is upon the development of dyschesia with a loss of the defecation reflex The institutionalized patient having this form of constipation is subject to fecal impaction Neurologic patients are particularly prone to this occurrence If this condition is unrecognized such patients are subject to either intestinal obstruction or alternate periods of diarrhea and constipation The administration of antidiarrheal agents in such instances

TABLE 1

CLASSIFICATION OF FACTORS RESPONSIBLE FOR CONSTIPATION IN INSTITUTIONALIZED PATIENTS

- I Institutionalization itself
  - A Psychological
  - B Environmental
    - 1 Unsatisfactory facilities
    - 2 Delay of toilet facilities
  - C Constipating medications
  - D Dietary restrictions and alterations
  - E Bed rest—postural requirements
- II Disturbances in gastrointestinal motility
  - A Inadequate stimulation
    - 1 Chemical
      - a Intestinal contents
      - b Medications
      - c Hormonal
    - 2 Mechanical
      - a Dietary
  - B Decreased excitability of gastrointestinal mucosa
    - 1 Disease states
    - 2 Medications
  - C Diseases of nervous system
- III Disturbances in act of defecation
  - A Previous improper training and neglect
  - B Previous laxative abuse
  - C Diseases of the colon or rectal mucosa
  - D Diseases of the anal sphincter
  - E Diseases of the nervous system
  - F Medications
- IV Disturbances in expulsive powers
  - A Atony of intestinal musculature
  - B Weakness of pelvic floor
  - C Inefficiency of diaphragmatic movements
  - D Weakness of abdominal wall muscles

be the result and/or summation of many actions Increased intestinal tone with diminished excitability and resultant decreased peristalsis delayed emptying of the stomach because of pylorus spasm increased absorption of intestinal fluid secondary to delay of propulson of contents and decreased secretion of mucus are the accepted explanations for opiate constipation Another factor previously unemphasized is that of diminished awareness of the patient of the need to defecate This is analagous to the patient s analgesic response, whereby there may be an increase in peripheral pain threshold and a change of the patient's reactivity to noxious stimuli

Many medications in current use for the treatment of gastrointestinal disorders may be exceedingly constipating Preparations containing aluminum silicates, kaolin astringents of all types and bismuth salts may result in hard fecal masses which may lead to fecal impaction Incidentally the simultaneous administration of opiates (as in the case of cough syrups) with these medications should be avoided because of the possible occurrence of intestinal obstruction The passage of these scybalous masses through the anal canal many aggravate the constipation because of anal spasm secondary to irritation of pre existing anal lesions Many patients also lack the expulsive power required for the passage of such stools Since the usual cathartics are of limited value for this form of constipation the likelihood of dry hard stools occurring

PROCTOLOGIC ASPECTS OF CONSTIPATION AND DIARRHEA

By Robert Turell

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This paper will discuss from a broad biologic standpoint, the various proctologic aspects including the complications of diarrhea and constipation

Diarrhea

Diarrhea from any cause even of short duration may produce proctologic complications Significant complications are most usually observed however in diarrheas of long standing as in chronic ulcerative colitis Cancer of the colon and rectum is the most important while infections of the anal structures are the most frequent complications [1] It should be recalled that the anal ducts which usually empty into the anal crypts of Morgagni lead to racemose multiglandular structures situated in the perianal tissues even piercing the sphincteric musculature The columnar epithelium lining the anal ducts is cuboidal in branches and under suitable conditions may become a natural incubator for bacteria Infection of the anal crypts anal ducts and anal glands occurs frequently as a result of the mechanical deposition of infected usually liquid fecal material within the anal crypts which may lead to the eventual development of perianal and perirectal suppurations eventuating in anal fistulas

Conservatism is practiced whenever possible Operations for subacute or chronic anorectal lesions accompanying diarrhea such as hemorrhoids or anorectal fistulas should be delayed until the underlying disease of the colon is either controlled or eradicated with the possible exception of chronic anal fissures (ulcers) which because of the excruciating pain they frequently produce may demand surgical intervention On the other hand acute situations such as suppurations should be accorded prompt drainage by incision and wide unroofing of the abscessed cavity both to prevent further spread of the suppurative process and to relieve the accompanying pain Acute anal fissures or exacerbation of chronic fissures that do not respond to conservative measures such as hot hip baths and the topical application of cocaine or its derivatives (which incidentally are strong cutaneous sensitizers) may necessitate immediate surgical intervention Low or even high anal fistulas are best extirpated at a propitious time

The irreversible pathologic changes of the colon such as shortening of the gut stricturization perforation pseudopolyposis and massive hemorrhage encountered in chronic ulcerative colitis are mentioned but will not be discussed

A solitary adenomatous polyp unlike a pseudopolyp observed in association with ulcerative colitis or amebic dysentery that is situated within the reach of the endoscope is managed in the same manner as is such an adenoma occurring in normal colons However frequent posttherapy endoscopic supervision is more urgent in these patients for the earliest detection of recurrent or new adenomas which have a great propensity to undergo malignant degeneration It should be stressed that while cancer in ulcerative colitis frequently begins in an adenoma [2] it certainly develops very often in the absence of any visible

may precipitate serious consequences. Measures to increase intestinal motility have not been successful for this type of constipation. Water retaining colloid or hydrophilic preparations are of greatest value in such cases. A maintenance of a soft stool is of considerable help not only because cleansing enemas are facilitated, but also because rectal irritation and anal lesions may subside under such a regimen.

Disturbances in expulsive powers are rarely the sole reason for constipation. Such factors may be primary or secondary to other etiologies already discussed. Correction of these expulsive powers may not be possible but the consequences of the resultant dyschesia may be prevented by fecal softening agents. Addition of stimulating laxatives is also of help.

In summary the institutionalized patient presents many reasons for disturbances in bowel function. Treatment with cathartic agents alone without consideration of the various factors which may be responsible is inadequate and may only perpetuate the condition. Emphasis should be placed upon the institutionalization itself as a major contributing factor for chronic constipation. The problem of complete bed rest and the administration of medications which may be constipating are the most important in this regard. Change in consistency of feces to hardness with resultant dyschesia is of greater significance than temporal alteration. Preparations that retain water and thus maintain a soft stool are of the greatest value for the treatment of constipation of the institutionalized patient.

are incidental or etiologically directly contributory to the occurrence of carcinoma in the diverticular sigmoid colon

Infrequently functional constipation or constipation on a habit basis is an important added problem to the existing constipation or more correctly, to the obstipation encountered in incomplete colonic obstruction caused by organic conditions such as extraintestinal lesions (genitourinary disease and adhesions) or intestinal conditions such as kinks or angulations partial intussusception ameboma, megacolon stricture and benign or malignant neoplasms

Megacolon associated with severe chronic constipation may be divided into two distinct general types (1) true Hirschsprung s disease (aganglionic or achalasic megacolon) and (2) functional (idiopathic) megacolon In Hirschsprung s disease there exists an obstructive neurogenic narrowing of the rectosigmoid which is caused by the absence of parasympathetic ganglion cells (Auerbach s plexuses) which in turn results in a radiographically demonstrable lack of peristasis in that segment of the terminal bowel[9] causing intractable constipation practically from birth The narrow distal aganglionic (achalasic) segment of the gut varies in length starting in some cases near the anus and extending high up in the left colon beyond the rectosigmoid which is the usual site of involvement The present-day accepted definitive therapy is a one stage resection of the narrow aganglionic segment of the bowel distal to the dilatation and anastomosis of the two ends of the bowel with preservation of the anal sphincter muscles[10, 11, 12] Medical or conservative therapy is only of temporary or adjunctive value

Although the true pathogenesis of the functional (idiopathic) type of megacolon is still undetermined it has nevertheless been separated from Hirschsprung s disease on clinical radiographic and histologic grounds[13] In these patients the real source of obstruction is the fecal impaction which may be the result of faulty training and care of the colon during infancy and childhood[14] The roentgenologically demonstrable narrow distal segment of the bowel is absent in these cases and hence they are not amenable to the same operative procedures In fact except for complications such as volvulus this condition seldom requires surgical intervention as it invariably responds to medical management It should be stressed however that the use of enemas for the treatment of constipation in all megacolonic cases may be followed by sudden and unexplained fatal collapse[15] Tap water used for enemas may produce an unheralded water intoxication and a fatal electrolytic imbalance especially of sodium There may occur a sharp fall in the plasma sodium chloride and proteins and an elevation of the plasma volume It is thought that tap water is absorbed more readily from the dilated gut than from the normal colon Isotonic saline solution or gelatin solution in a concentration of 7 per cent should be substituted The last solution is especially suitable for nephritic or cardiac patients in whom the use of saline solution is not advisable[15]

Congenital obstructive anorectal malformations may also produce constipation of varying severity which sometimes results in what has been termed organic megacolon[14] Important in these anomalies are the congenital strictures and bands that are situated near or at the pectinate line which are the result

or recognizable antecedent neoplastic mucosal lesion [3] It is possible that antecedent adenomatous tissue may be destroyed beyond recognition by the malignant process

Because of the great malignant potentialities of adenomatous polyps associated with long standing ulcerative colitis solitary adenomas when situated above the reach of the 25 cm scope, should be accorded strict individualization, colectomy is desirable if not mandatory Multiple adenomas are best treated by total colectomy because the chances for the development of malignancy are multiplied or compounded by the number of adenomas present

Cancer, with or without an antecedent adenoma, usually occurs a long time after the onset of the colitic process, and occurs even following the performance of an ileostomy or subtotal colectomy Furthermore cancer arising in ulcerative colitis is anaplastic and of high grade malignancy, it metastasizes early, and is rapidly lethal The therapeutic implications are of course obvious

Pruritus, anal or anogenital may be produced by diarrhea from any cause and is usually but not always attributable to the local irritative effects incident to the passage of loose feces With the improvement of the diarrheal condition the pruritus disappears or its intensity is greatly diminished Therapeutic agents such as corticotropin (ACTH) or cortisone, that tend to influence favorably the colonic process also effect similarly the pruritus in some of these patients [4] Local therapy is only of adjunctive value

Since the advent of the broad spectrum antibiotics the proctologist has been confronted with a new anorectal syndrome consisting mainly of diarrhea or pruritus or both Fatal staphylococcic enteritides [5] [6] have been reported but up to now these have occurred in hospitalized patients only My observations concur with those of Pappenfort and Schnall [7] who believe that pre existing skin and mucosal lesions probably are important predisposing factors " as I have noted approximately 80 per cent of my cases had pre existing anorectal disease I am also in agreement with Kligman [8] that this syndrome may be the result of 'superinfection with antibiotic resistant microorganisms including both fungi and bacteria ' The treatment of the diarrhea is simple in most cases probably because of spontaneous recovery and intractable for some time in some instances The therapy of pruritus on the other hand is more refractory The newer antibiotics, such as erythromycin [9] and magnamycin may be effective against the staphylococci that have become resistant to the broad spectrum antibiotics

Constipation

Retention of feces particularly of dry stool in any segment of the left colon may result (1) in the development of volvulus especially in the sigmoid colon in individuals who have elongated pelvic colons (2) in the reactivation or perhaps causation of sigmoidal diverticulitis in some individuals and is probably produced by stasis in the normally narrowed lumen of the sigmoid colon, (3) in mucosal irritation manifesting itself as a constant mucosanguinous discharge or (4) in the occasional occurrence of serious trophic ulcers In diverticulitis there exists considerable uncertainty as to what extent the foregoing factors

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of the incomplete dissolution of the membrane between the hindgut and the proctodeum, as well as postoperative strictures following corrective procedures performed for imperforate anus The congenital strictures may be soft pliable, dense circular semilunar and large or small calibered Most of the soft strictures disappear spontaneously Some however require periodic digital dilations Utmost gentleness should be practiced in these dilations lest mild or moderate shock result The semidense or fibrous strictures usually fail to respond to dilations and require surgical intervention Since 1942 I have been employing electrosurgical resection using a high frequency double loop resector [1]

Anorectal lesions which produce spasm of the anal sphincteric musculature usually cause constipation which lasts for the duration of the underlying lesion Many of these same anorectal conditions also can be produced by the passage of liquid stool which is the result of habitual use of cathartics or the injudicious use of liquid petrolatum Cathartic drugs may cause an irritating effect upon the anal canal, may induce passive congestion and may cause the deposition of bacteria laden feces in the anal crypts Newton and MacGregor[16] have described 'a clinical entity of spasm and fibrosis of the sphincter ani with marked constipation chronic excessive use of cathartics and so forth for which they advised anal dilatation with or without partial division of the external sphincter Morton[17] has subscribed to the foregoing concept and observed this syndrome in 90 patients Other authors[18] have referred to this condition as pectenosis which is a misnomer My own studies[1] have shown that this syndrome in some cases is produced by dysfunction of either the subcutaneous component of the external anal sphincter muscle or the muscularis submucosae ani [19] which is a distinct muscle situated in the region of the pectinate or dentate line The role played by the latter muscle is not that of a fibrous band but that of a muscle band exerting its effect through either spasmodic contraction produced by local irritation or hypertrophy resulting from chronic spasm and leading to stenosis In other persons inflammation and infection of the anal glands ducts and crypts with resultant fibrosis involving the subcutaneous component of the external anal sphincter muscle are responsible In the occasional individual this syndrome may be the outcome of an anxiety determined hypertonus of the anal sphincter [0 21]

It is also pertinent to call attention to the fact that oft recommended treatment of digital or instrumental dilation of the anal canal even when performed under anesthesia is a traumatic procedure that sometimes causes sufficient hemorrhage to produce recurrent fibrosis A formal sphincterotomy not to be confused with the so called pectenotomy is the preferred treatment [23] This operation because of the smooth convalescence and the inevitable successful issue is definitely preferable to the ill conceived pectenotomy or sphincteric dilation, digital or instrumental

The foregoing remarks apply equally to the consideration of chronic anal ulcer or fissure which is another important complication and/or a cause of temporary constipation This anal lesion it should be stressed is caused either by defecatory trauma brought about by straining incident to the passage of hard stool and/or inflammation and infection in the preformed anal structures already discussed It is best treated by wide excision of the ulcer bearing areas in

cluding the involved crypt or crypts and followed by the classic or modified sphincterotomy [23] This simple operation is definitely preferable to taking even the slightest risk with the injection of slowly absorbing anesthetic agents which are neither anesthetic' nor devoid of hazards [24] [25]

I am unimpressed with the belief that uncomplicated hemorrhoids *per se* are either the cause or a complication of constipation On the other hand prolapse of existing internal hemorrhoids or of the colorectal mucosa is observed rather frequently in constipated individuals In many cases prolapse is the likely result of straining at stool necessitated by the presence of anal spasm or narrowing produced by factors already described

Prolapse of the rectal mucosa in children is very frequently associated with constipation and is aggravated by the ill advised use of laxatives

Megarectum incorrectly called rectal dyschezia or rectal constipation is a dilation of the ampulla occurring in children and infrequently in adults It is most likely the result of a neuropathologic process resembling megacolon Patients so afflicted have no urge to defecate resulting in the accumulation of hard feces in the rectum Use of drugs is quite ineffectual and resort must be made to enemas Treatment remains discouraging but in children time growth and physical development produce some improvement [26]

Rectal impaction of feces may manifest itself as fecal incontinence or a continued liquid fecal discharge or even diarrhea It may occur (1) as a result of any lesion that produces anal sphincter spasm or anal stenosis (2) in debilitated bedridden persons who lack rectal expulsive power or (3) following the use of barium sulfate either taken by mouth or given per rectum for diagnostic purposes The long range treatment consists in the removal of the cause while the employment of oil retention and cleansing enemas is an immediate therapeutic necessity At times digital or instrumental removal of the impacted stool is necessary This maneuver sometimes necessitates the employment of some form of regional anesthesia

Laxatives have no place in the therapy of constipation caused by organic etiologic factors I believe with Ogilvie[27] that in the absence of organic causes normal defecation usually comes from equanimity and common sense Hardly ever do I find a need for cathartic drugs in the management of the noninstitutionalized cooperative patient afflicted by constipation from any cau e the implications of some studies [8] to the contrary notwithstanding This statement also applies to the use of suppositories[1] or rectal dilators [9]

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DOCTOR QUIGLEY What percentage approximately of individuals who have been shown to have malignancy of the colon tried self medication with cathartics? To what extent has this self medication with cathartics delayed recognition of malignancy? Does it delay it to the extent of a month or six months or a year? It is very difficult information to get and if any one can help me I shall appreciate it greatly

CHAIRMAN JORDON Doctor White s and Doctor Machella s papers interested me greatly with reference to our previous discussion in which the ulcerative colitis was described entirely as a psychotic disease and we reached the point where psychoanalysis was suggested if not recommended Doctor White made the statement that there was a retrogression to immaturity in the disease and that this one personality defect which is stressed so much in ulcerative colitis tends to disappear after the diseased colon is removed I believe that too He did however mitigate the statement a little by saying that the patients went on with a perfectly normal life in spite of the fact that they must have some inherent personality defects to have had the disease Doctor White I should appreciate very much if you would tell us whether you really do believe that in the case of a young student at college doing very well on the Dean s list and happy suddenly comes down with ulcerative colitis it is a personality defect? Your observation that it disappears with removal of the disease is a very admirable one

Then I should like to ask whether or not the use of cortisone or ACTH has produced gastric ulcer in any of these cases and what the opinion is about the relationship of malignancy to ulcerative colitis In our experience we have had a great deal of fear about the young patient who has had the disease over ten years That seems to be the group in which malignancy has occurred I think Doctor Machella said he was worried about the boy who improved so much In one area in the descending colon was it there was a question of carcinoma that worried you?

DOCTOR WHITE Doctor Jordan I am afraid you caught me in the midst of two conflicting statements that I was not aware I was making I do not know the role of the personality and emotional problems with regard to the etiology of ulcerative colitis I have tried to look at the personality problem in three ways (1) to size up the person that one is dealing with who gets ulcerative colitis (2) to analyze the situation which appears to precipitate the attack of ulcerative colitis if such seems to be the case particularly the type of situation where the patient has withdrawn from the support of an older individual to whom he has a peculiarly ambivalent relationship and (3) what the psychiatrist might call the mental status of the individual at the time that he is sick As I look at these patients I think that the psychiatrists are basically right that a large percentage of them are people who are dependent who are not very aggressive who are deriving satisfaction and security from an attachment to an older individual who is usually a parent or a parent substitute such as a teacher and that often when this person is withdrawn there is a tendency to produce tension and possibly aggravate the disease When the patient is really sick and

one looks at the mental status in the cross sectional sense, as the psychiatrists say then one sees a patient who is depressed and whose behavior is childish petulant, and negativistic He looks like a miserable specimen of humanity without any future at all Correct or not, my thesis is that, when the exacerbation of ulcerative colitis is over, whether through spontaneous remission or medication or as the result of one of these surgical procedures the mental status clears up, but that the basic condition remains unchanged

With regard to your second question which had to do with cortisone causing gastric ulcer, I should say that I am well aware of the published statistics which indicate that there is a significant incidence of such ulcers but we have not actually seen one ourselves

CHAIRMAN JORDAN Carcinoma

DOCTOR WHITE Again I am aware of your figures and those of Doctor Barton which are in the neighborhood of two to two and one half per cent Our own series is very small I recall one distinct incident, but I could not give you any personal experience on that point

DOCTOR MACHELLA I agree essentially with what Doctor White said, but I disagree with both of you that the ileostomy and surgery procedures alter these individuals, and that they are different after operation Sometime I am going to add up the total number of days that our patients spend in the hospital after an ileostomy and compare it with the time they spent there before it I am sure I know how it will turn out I have never seen an ulcer developing in our patients who have had regional enteritis or ulcerative colitis and who had been on cortisone treatment for varying lengths of time up to two years I have reviewed most of the cases that have been published in which it was claimed that cortisone was responsible for the development of the ulcer I must confess I should hesitate to go before a critical jury with any of them

The reason I am worried about the boy mentioned is because he seems to have an area of pseudopolyposis in the descending colon and that is the thing that worries me tremendously about these patients If they are going to develop carcinoma then I wonder whether we are right in persisting in treating them for a long period of time particularly those that do not appear to do so well

In our own experience the incidence of carcinoma of the colon in chronic ulcerative colitis has been extremely low I can recall two cases in the world s literature as I have been able to review it In covering some 6 890 cases the incidence of carcinoma of the colon was three per cent I admit that figure must be corrected for the natural incidence for it depends upon how the figures are collected

Doctor Kiefer of Boston had a very interesting set of figures He had two series of cases in one of which the diagnosis was made on the basis of pathologic reports and on sections removed at operation There the incidence was somewhere around 4 2 per cent In the other series in which the diagnosis of carcinoma was made by the usual barium enema and sigmoidoscopy the incidence was about half that

DOCTOR INGELFINGER To get back to the national neurosis again I agree with Doctor Seymour Gray and his predecessor who commented on laxatives They divided their cases into a first group having anxiety about the type of

stool and a second group struggling with diet consciousness versus bowel consciousness I think the difference there is that the patient gets somewhere with his diet consciousness and gets only into trouble with his bowel consciousness

DOCTOR TURELL I was interested in Doctor Batterman s statement that individual peculiarities should be considered even in institutions I wonder if it might not be a good plan for all hospitals to adopt the plan of not passing around the laxatives indiscriminately but finding out who actually does need one

CHAIRMAN JORDAN Doctor Turell I should like to speak of our experience with patients having so-called anal spasm probably the milder forms which we see so often with chronic laxative use We formerly thought they were candidates for immediate dilatation We find with medical management and the use of hot compresses to the anus that spasm is relieved just as the symptoms of the irritable colon are relieved

DOCTOR BATTERMAN I should like information first in regard to personality traits that are associated with ulcerative colitis I have to admit in my experience with colectomy that the patients have an extraordinary change in the personality for the better It brings up the question whether the psychosomaticists are correct or not These individuals will direct their channels for psychiatric changes to other spheres of influence in the body and I wondered if any of the ulcerative colitis patients had colectomies if they developed diseases which would be considered in the psychosomatic sphere to go along with the psychosomatic viewpoint that they might develop other channels

The second question I should like to raise is that of therapy Many of these ulcerative colitis patients as Doctor Turell has pointed out have anal and rectal lesions and as part of the general management of this particular area it is very important because this sets up a reflex, increased motility of the higher intestinal area and the patient may have diarrhea perpetuated on the basis of anal lesions By simply clearing up these lesions by perhaps using local anesthetics there or bland ointments we have been able to cut down the diarrheal movement to two or three a day where previously they were up to ten or twelve Should this not be part of the general management? It does not clear the ulcerative colitis but makes the patient more comfortable

DOCTOR GRAY Suppose I were to select ten physically healthy medical students ten patients with irritable colon ten patients with ulcerative colitis and ten patients with peptic ulcer could they be distinguished from each other on personality type? Psychiatrists have pointed out classical personality types for each group and when I have talked with them I have said I shall send you one ulcerative colitis patient and one ulcer patient both adults and I believe you cannot tell me which is which I have yet to get anyone to take up the challenge The question is do psychosomatic influences alter the disease process or are they the cause of the disease? I think that is the primary problem that we have to face Doctor Jordan s question about ulcerative colitis and ulcer is exceedingly interesting because we know that ulcerative colitis patients rarely have peptic ulcer The incidence of ulcer in ulcerative colitis is less than in the population at large I have seen one case of proven ulcer in a

patient with ulcerative colitis In general, it is rare So there is the problem of local tissue resistance, and that is an important question in regard to the cortisone In our experience cortisone or ACTH have not produced peptic ulcer probably for two reasons (1) that the endogenous output of the adrenal in a chronic debilitated patient with ulcerative colitis is definitely decreased His steroid output is decreased and, therefore, he probably will not get the same response, secondly that there is some change in local tissue resistance With regard to the stomach I should be glad to present Doctor Machella with some autopsy material on gastric ulcers, following cortisone therapy Personally I know of at least six or eight different physicians who have had patients develop gastric ulcer and hemorrhage while these patients were on cortisone therapy So there is some cause and effect relationship there although the ACTH patients probably have a higher incidence

CHAIRMAN JORDAN I assume that Doctor Gray means the ulcerative colitis patient is in remission and appears well, and the peptic ulcer patient, perhaps, likewise? They are not sick in bed In other words my answer to the question as to whether we could differentiate would be No"

DOCTOR GRAY That is right

DOCTOR MACHELLA Probably I would come out pretty well in this test I am not a psychiatrist and I do not understand the language But I think if I talked to these people I could figure out which disease they had I always say if I want to get a job done somewhere there are two types of patients that I would take I would take ten ulcer patients rather than ten ulcerative colitis patients If I took ten ulcer patients with me I would get the job done If I took ten ulcerative colitis patients with me I would have to do the job for them

CHAIRMAN JORDON Is that the nature of the disease or the person?

DOCTOR INGELFINGER I think I could tell an ulcerative colitis patient most of the time the others not

DOCTOR WHITE Of course, the classical overcompensated aggressive ulcer personality statistically is only found in approximately one third of the ulcer patients, so that there is no sharp delineation between these types at best In general I would agree with Doctor Machella s characterization of the two groups

Now about the question of substituting another symptom for the colitis after removal of the colon we have not seen that We have seen people continually have their difficulties (in fact I have one lady in the Virgin Islands getting a divorce) but as far as we know these are not hysterical symptoms which have a specific meaning The removal of the symptom does not necessarily leave the patient with the need of another

DOCTOR BATTERMAN Not being a psychiatrist I think one should use a group The same mystical figure of 75 per cent comes up representing psychosomatic disease and it is a wonder that the body can channel itself in a different direction Where one has tremendous psychosomatic aspects compared to the ulcerative colitis they are not associated very often in the same percentage I would be in accord with Doctor White I think many of the personality

changes we see are secondary to the disease and not causative factors Whether one removes the cause of the disease or not you would have them

DOCTOR ALMY We actually have in our clinic a little joke We call it the waiting test Unfortunately most of our patients wait an hour or two before they are seen and when the fourth year students come in for a stay in the clinic I ask them to decide whether they think the patients with ulcerative colitis or the patients with ulcer complain the more when they are kept waiting The voting is entirely in favor of the patient with the ulcer I have never had a single student who said that the ulcerative colitis patients are the complainers I think this result reflects a personality difference It obtains at times when they are active as well as when they are inactive

CHAIRMAN JORDAN Aren t you a little surprised at the way that turned out? I should expect the ulcer patient to rage about it

DOCTOR ALMY That is the way it did turn out The patient with the ulcer complains The patient with the ulcerative colitis is apparently just delighted to wait for you

DOCTOR WHITE I also use the test which we call the picture test I bring the students in and I tell them that there is a case of ulcerative colitis in one of the rooms where I have purposely upset one of the pictures on the way and then I say Now let s go in there and we are going to find that picture straightened out You invariably do The ulcer patient doesn t do it

DOCTOR INGELFINGER Doctor Gray and I know some patients in whom it would be extremely difficult to detect that they had ulcerative colitis One of them is a young lady that both he and I know She looks well and if you talk to her casually you would not think of that diagnosis.

DOCTOR GRAY The reference is to a little girl that we have been following up now going to college It is a case of long term cortisone therapy She has been on it now almost a year and one half If she were an adult a diagnosis would not be difficult, because they are more inclined to very severe headaches or arthritis or backaches or many of the other psychosomatic complaints characteristic of adults But in the case of a young girl who complained as this girl does or a young boy I should think of ulcerative colitis rather than ulcer just on the age basis In an adult group from the pure psychosomatic standpoint it is exceedingly difficult to differentiate As to the test of tipping the picture it seems to me that the ulcer patient should have upended it Such patients are compulsive flicking the dust off the furniture They are tidy The ulcerative colitis patients are characteristically in the high intelligence group hard working aggressive in the top of the class in law school for example They come in during examination periods with acute exacerbation of the ulcerative colitis But this little girl Doctor Ingelfinger and I are interested in after being sick went out on her own and took an aptitude test for college which I though was absurd Apparently she had no chance of getting in having had hardly any schooling Nevertheless she got in with flying colors Yet we know the ulcer patient is the same type executive the hard driving type There is a tremendous overlap and I don t see how one can tell I agree too that the ulcerative colitis patient, when he is well is a pretty normal person

I have seen such patients, after ileostomy, go out, have three or four children and lead a pretty normal healthy life I know two patients, who are a married couple who both had ileostomies and colectomies and yet got along well and with no complaints They brought up children none of which have had ileostomies They are perfectly normal people and apparently do not convert to other forms In my experience, they do not if they are well If they are chronically ill, that is something else

About the waiting test, if the ulcer patient is under good management, he will get well quickly, within 24–48 hours The ulcerative colitis patient is sick, anxious to get care love and attention After he is well I think he will be just as impatient as the ulcer patient I believe it depends upon what state they are in when they come to the clinic As we all know an ulcer patient, during the first visit is fairly asymptomatic if he stays on the diet reasonably I do not want to disparage the importance of the psychological factors in the treatment of ulcerative colitis, because I am an amateur psychiatrist like all good doctors are, and the psychological points are extremely important in the management of the patient, but does that mean that the psychological difficulties cause the disease? I really don't know and that is why I should appreciate hearing your thoughts on it

CHAIRMAN JORDAN Thank you Doctor Gray, for helping out in the defense of somatic psychic influences

COMMENT Interestingly enough in Doctor Machella s paper after he improves the one disease he develops a coronary He improves one organ and the emotions are channeled to another

DOCTOR MACHELLA That may have been what happened I don t know I know this patient had apparently a high enough blood cholesterol to get gall stones She was 46 years old when she got the coronary occlusion Whether that is what happened I don t know

ANOTHER COMMENT This remark may not be a happy one but in listening to the papers presented and to the discussion one gets the feeling that here we have a number of perfectly good doctors who are really trying to be amateur psychiatrists instead of getting down to some fundamental points in facing a sick patient with an anal spasm There is a spastic muscle with certain biochemical bases and the question arises as to whether there is enough adenosine triphosphate to supply relaxation a question of the Krebs s cycle a question of the balance between the sacral autonomic and sympathetic We do a great deal directly by influencing the sympathetic We can stop an anal spasm in seconds by blocking the sympathetic for instance at the nasal ganglion which is an easy approach This is one of many things that can be done

Then there is the question of calcium balance This patient with all these psychiatric manifestations who is under stress has definite biochemical effects of stress which in their simpler form may be just a matter of calcium balance and the injection of calcium ascorbate will do more for the patient than the experiment of seeing whether he would turn the picture on the wall We have reached a very serious position in our own profession when as physicians trying to do amateur psychiatry we leave the patient pretty much at loose ends

I am striking this note to indicate how important it is to tackle a spasm a

colitis or an ulcer primarily on medical grounds that is from a biochemical and physiological viewpoint and if the psychiatrists have something to contribute let them do so on top of a biochemical basis

CHAIRMAN JORDAN That is a very noteworthy comment I should ay that in our discussion of anal spasm at least in the remark that I made we were treating the physiology with our suggestions for treatment, the bowel management routine and the applications of heat and rest so that although we left the biochemistry out of it we did treat physiology and possibly biochemistry follows along Would that be a possibility?

DOCTOR INGELFINGER I should like to make a strong rebuttal I should like to say that what advance we have made in recent years in medicine is twofold One is the recognition of biochemical abnormalities but the other is the appreciation so often emphasized in this discussion that you cannot treat a patient only for calcium deficiency adenosine triphosphate abnormality or anything like that The patient is more than that

DOCTOR MACHELLA I agree Of course the surgeons have presumably made an attack on this disease on a physiologic basis and have succeeded in following up the environment with the method of treatment I think what treatment has been made in ulcerative colitis in the past few years has been made along the psychosomatic lines I don t think anybody can deny that

DOCTOR GRACE I should like to make two comments (1) concerning the differentiation between the person with peptic ulcer and ulcerative colitis I think we all have to be aware that in examining one isolated group of people we become overwhelmed with the features we see in that particular disease For instance I have written down a number of things of behaviorally treated patients with ulcerative colitis in the past and I am not prepared to defend any longer the interpretation that meticulousness cleanliness and arranging pictures on the wall are manifestations of compulsive obsessive behavior and a part of the neurotic behavior in general and is not anything specific for that disease If you wish to quantitate it most people are people with migraine headache not ulcerative colitis or ulcer so I don t think that pursuing the personality features professionally is any longer profitable

Then the question always comes up Which is cause and which is effect? Do emotions cause disease? Do emotions cause symptoms or the symptoms cause the emotions? I think that one has to look upon things in a different way than that the reaction of the human being to a stressful life experience is the final adaptation to that threatening situation which involves his frame of mind which you can call his attitude or emotion For example when the individual is facing a circumstance with the feeling state that he would like to get out of here and run by moving his feet and legs to accomplish it he is at the same time having stiffness and contractions of the muscles of his back becau e he must fix the spine in order to move Now you cannot say that the patient s attitude is causing his muscles to be fixed His feeling tate as an adaptation to the circumstances of wanting to get out involves attitude towards and contractions of his muscles That is not cause and effect It is part of the adaptation that one sees in the viscera not part of cause and effect

CHAIRMAN JORDAN Doctor Grace before you go any further I am quite sure

that no good housekeeper, however healthy, could sit in a room, in a doctor's room, without straightening a picture

DOCTOR INGEGNO I am not one to belittle the role of the advances in understanding the personality of a patient in illness but I should like to have my colleagues indicate to me, in their experience, one patient in whom the treatment of ulcerative colitis, in which the psychosomatic aspects have been stressed, has not included bed rest blood transfusions and antispasmodics, sedatives diet, intravenous injections, and everything else Obviously, it is pretty hard to define which of these many modalities of treatment would be significant in an ulcerative colitis patient and, as a matter of fact, as has already been pointed out in this discussion, the best practice is the total approach including all these factors

In some cases of ulcerative colitis not all, I think the etiology is multiple

Doctor Andresen has stressed the possible role of allergy He thinks it is much more common than I do But certainly there is no doubt in my mind regarding some of these patients, for example with milk being the common offender You get the typical ulcerative colitis symptoms after milk Take patients off milk and the ulcerative colitis clears up You give them milk and they get the ulcerative colitis again That constitutes a certain proportion of these people Just how many I do not know I do not think it is the 80 per cent that Doctor Andresen suggests but the fact that he has stressed it as a factor should not be lost sight of It is perfectly simple in all of these patients at the beginning of treatment, to put them on five or six bland usually non allergic foods and then add one other food at a time to see what the effect of that particular basic diet is

Doctor Machella made a statement which really intrigued me He said that, in some of his patients he was convinced that psychosomatic factors were concerned, but that in some cases he failed to discover a problem If he failed to discover a problem how does one know that there is a problem?

There is another question If this sickness is known to be of much greater incidence in the young and middle aged, what happens in elderly patients? Why don t they get this disease too? Do they all become calm, phlegmatic, and accept everything?

CHAIRMAN JORDAN I am sure they do not in this day and age and I am glad you stressed the combination of somatic and psychiatric care in combination with those things Doctor Machella I am sure you would like to comment on that

DOCTOR MACHELLA What I meant to say is that in some patients, you cannot discover what the problem is but if you persist for a period of years, not infrequently you will get to the bottom of the situation I have worked on some of these cases for as long as three or four years before I finally found what the problem was

In my experience, old people get this disease just as readily as young people though perhaps in fewer cases Why that is I do not know Stress diseases may come on in younger people probably when responsibilities begin to accumulate

QUESTION Would Doctor Machella explain why the psychiatric treatment

is important? We had two patients in the general ward treated routinely with supportive treatment for ulcerative colitis They were transferred to the psychiatric ward and treated by very competent physicians and they perforated with the result that we don t transfer any more cases to the psychiatric ward We keep them on in the medical ward

Chairman Jordan I must say we had a similar experience with one case who had expert psychiatric care

Doctor Machella We had three patients that we referred to the psychiatrist who comitted suicide

Voices The psychiatrist?

Doctor Machella No the patients We had one other who after the first visit with the psychiatrist came back to his section picked up his clothes and has not been seen or heard of since If you are going to turn over a case to a psychiatrist you had better know to whom you are referring your case There are psychiatrists and gastroenterologists and automobile mechanics all kinds If you do turn a patient over to a psychiatrist you better be sure he is one who understands ulcerative colitis

Doctor Ingelfinger One other thing which I think most of us would agree on turning a patient with ulcerative colitis over to someone else is often one of the worst things you can do for him if he likes you has any respect for you I don t know what you think about it Doctor Jordan but certainly if you get a patient so that he gets along well with a member of the house staff and the latter leaves or some transfer takes place whether the patient is psychically attached to the surgeon or medical man that change upsets him greatly

Doctor White One more point at Mount Sinai Hospital in this city they have studied patients with ulcerative colitis in a very detailed fashion psychiatrically and it has been discovered that the patient with ulcerative colitis needs the support of his doctor and not only that he needs not to be dug at and probed at when he is in the acute fulminating state of the disease As Doctor Kaufman at Mount Sinai has pointed out in the early days of psychiatric treatment in ulcerative colitis when all the doctor did was to give moral support during the acute phase the patients did well but when his cases were treated by others many of them got into difficulties both psychiatrically and physically as the result of the psychiatric attention So that the mere fact that patients do not tolerate being taken away from their doctors and turned over to strange psychiatrists and probed at during the acute illness does not decry the importance of the emotional factor of the disease

Doctor Turell I never like to get involved in a discussion of ulcerative colitis However I have one question How long would you gentlemen continue your psychosomatic or somatopsychic treatment before turning the patient over to the surgeon?

Doctor Machella You have to evaluate the situation Sometimes I turn the patient over to a surgeon in an hour and sometimes in eight nine or ten months I do it when I am convinced that I cannot handle the problem for the patient in other words when the emotional situation appears to be beyond solution and salvage is necessary In one case I showed that the girl had high fever and diarrhea I would take her out of her environment and bring her